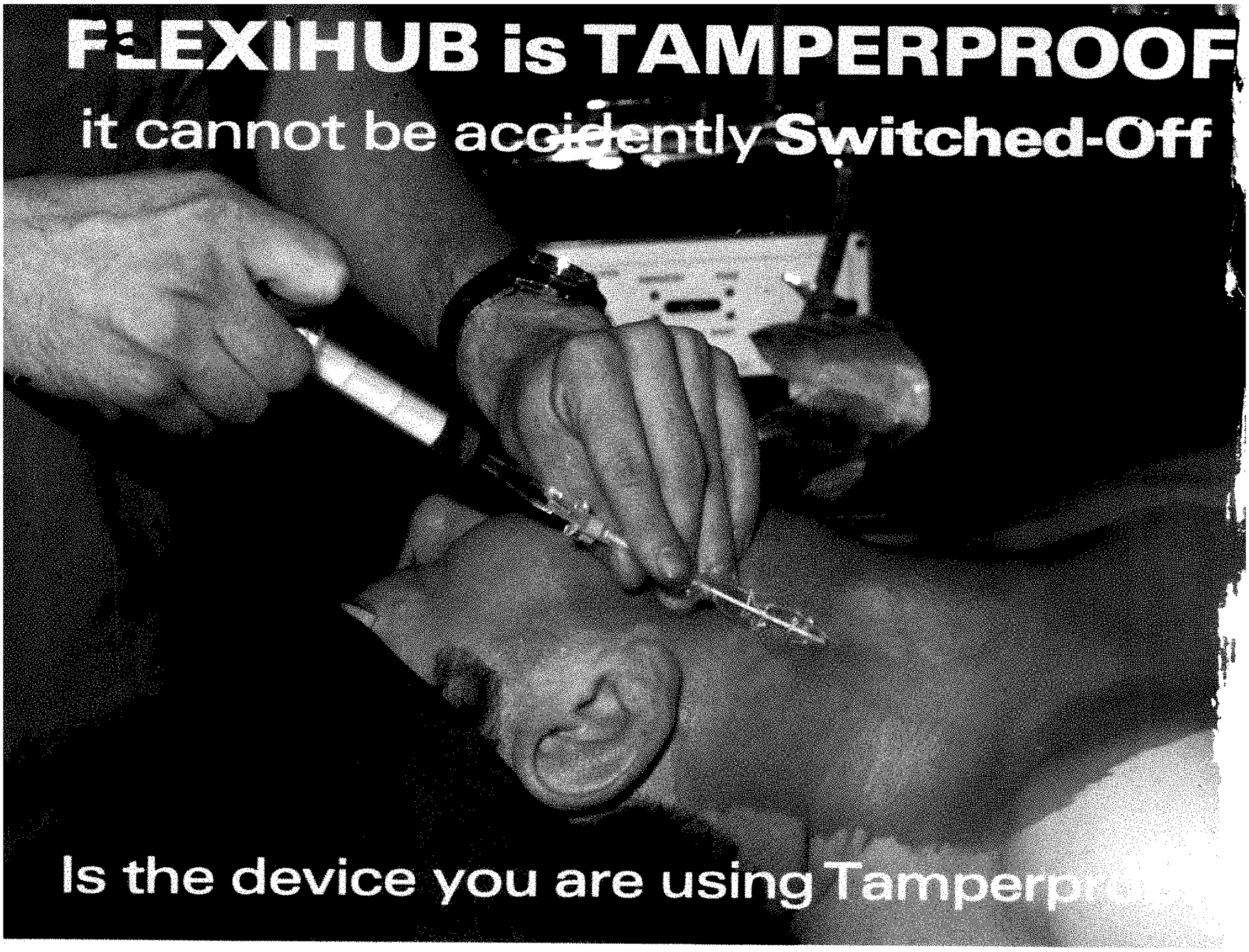
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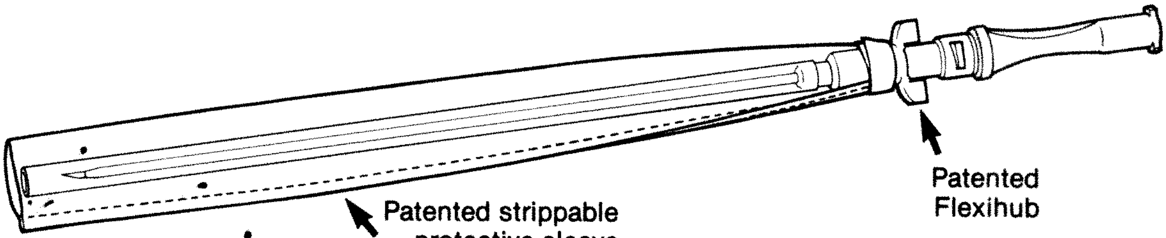

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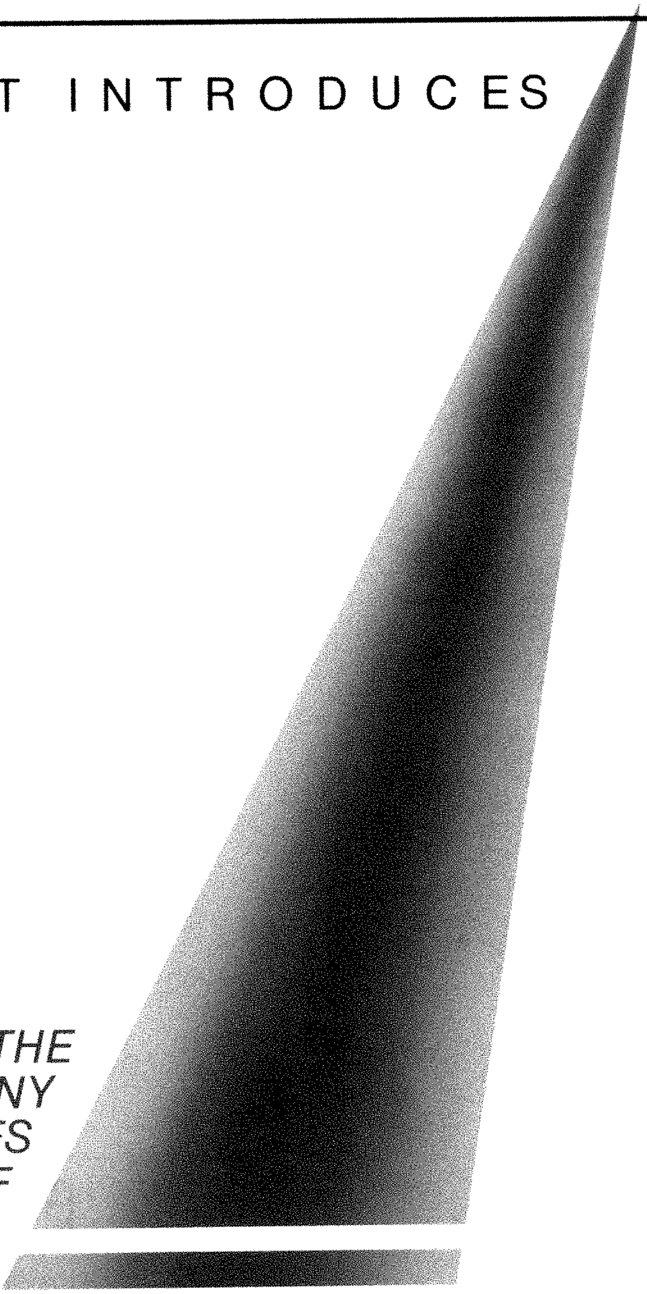

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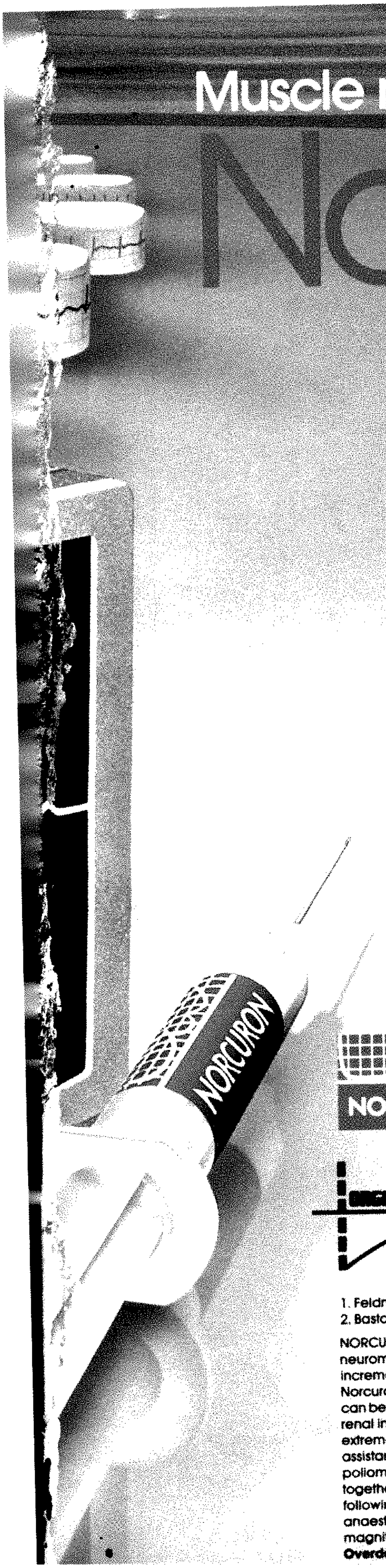

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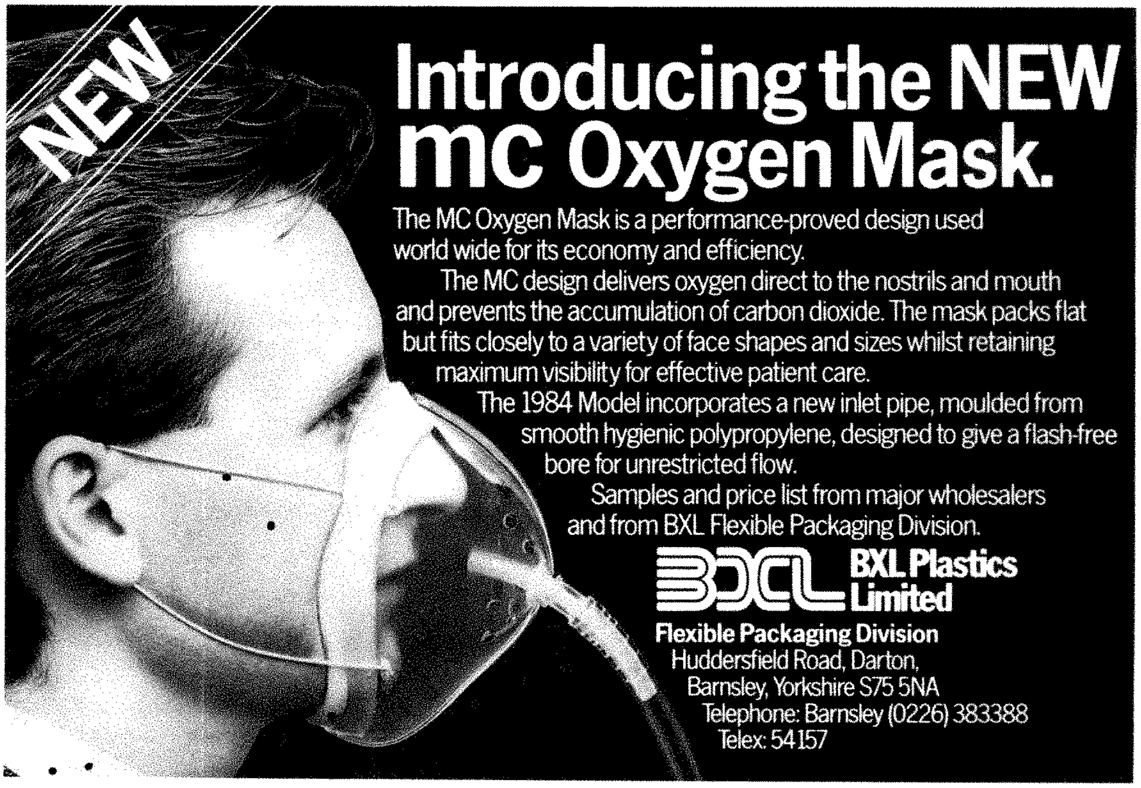

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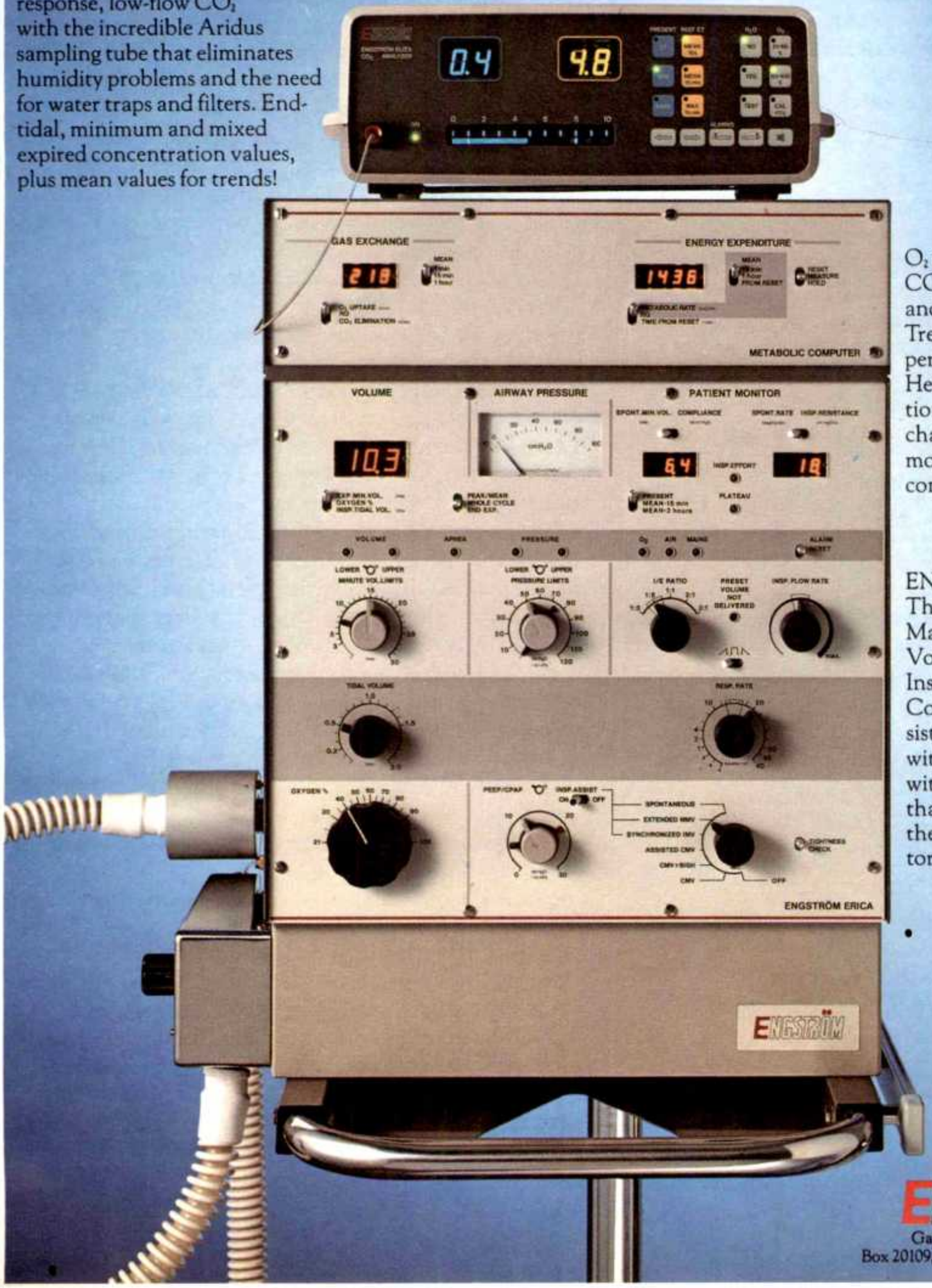

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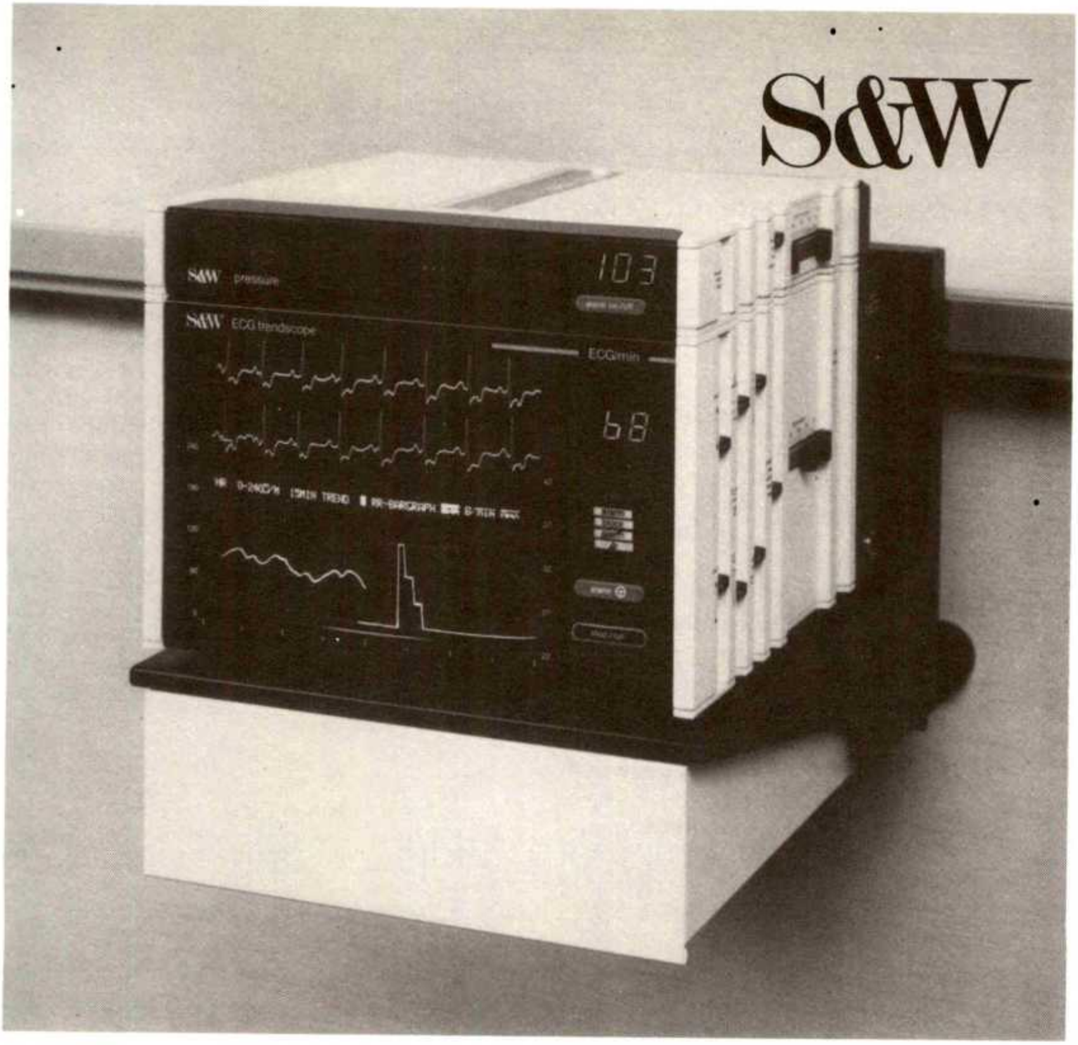

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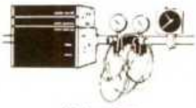
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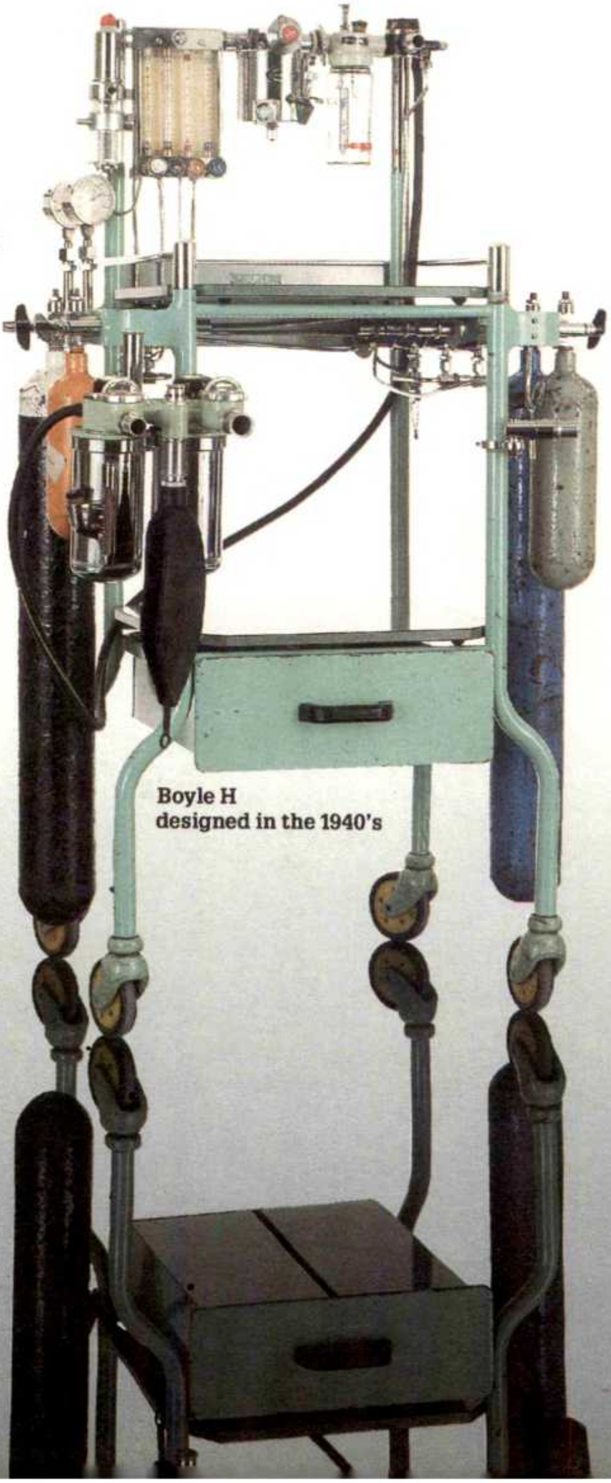

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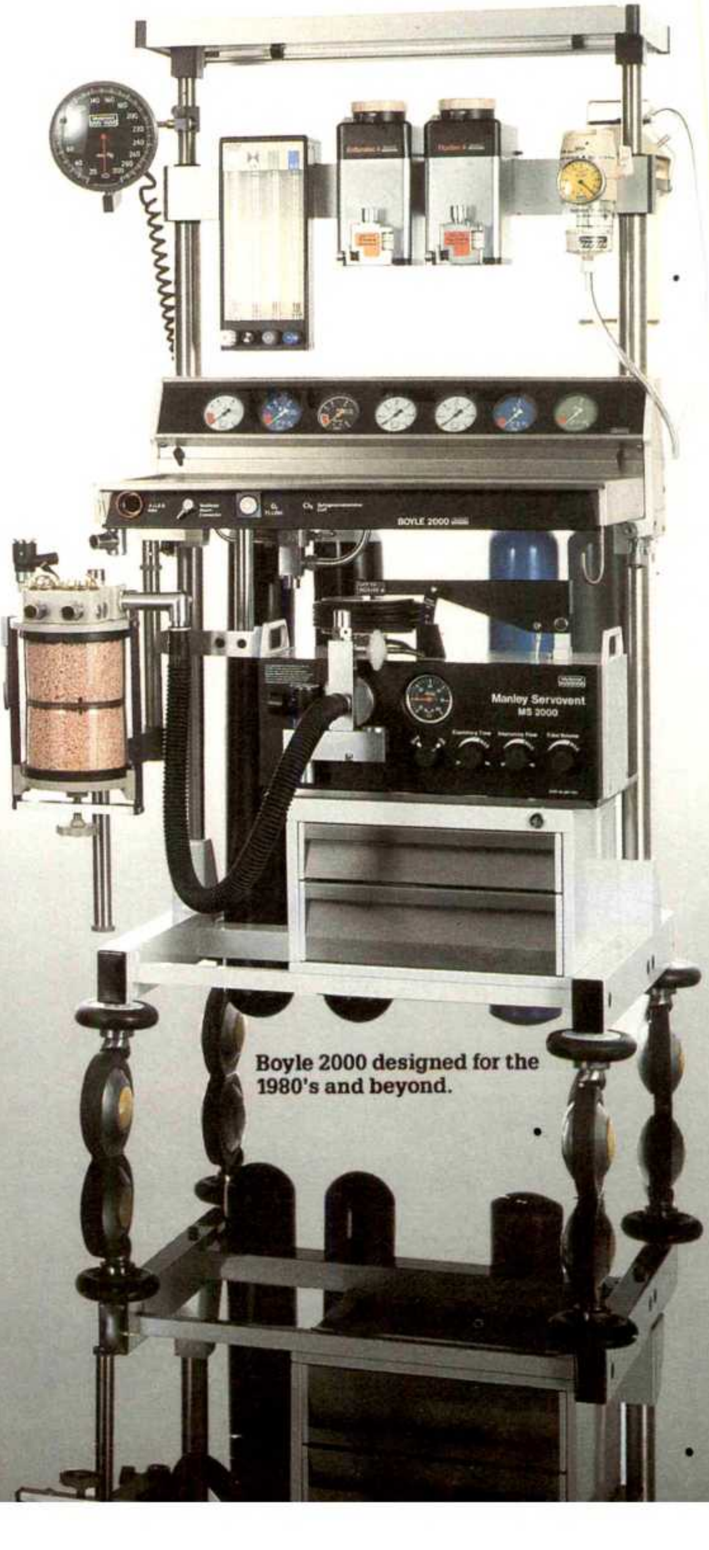

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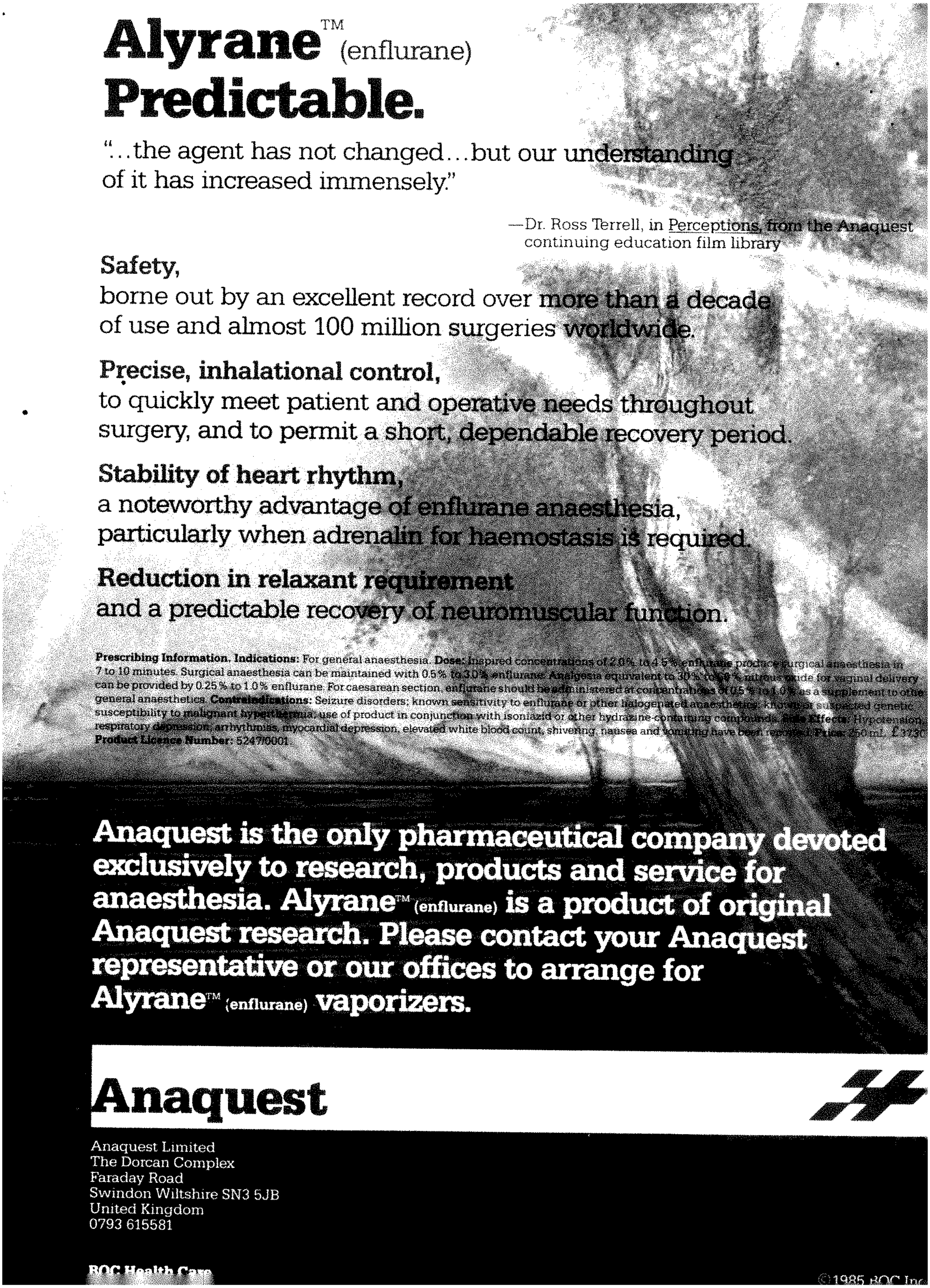

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 57, No. 7 JULY 1985

EDITORIAL

ANAESTHETIC EQUIPMENT

Although anaesthesia plays only a minor role in the overall morbidity and mortality following surgery, there is currently, and quite properly, a sustained pressure to reduce the potential contribution to the problems produced by the anaesthetist and his equipment. In the well publicized study undertaken by the Association of Anaesthetists, it was calculated that lack of equipment or equipment failure was responsible for 12% of all avoidable deaths wholly attributable to anaesthesia, as opposed to an error of judgement by the anaesthetist, which accounted for 70% (Lunn and Mushin, 1982).

In the U.S.A., Cooper and his colleagues have pursued the collection of data using the so called "critical incident technique" to assess the circumstances surrounding "near misses"—events which, had they passed unnoticed and unrectified, might have possessed the potential to produce morbidity or mortality. In 1978, they reported that equipment failure constituted 14% of all such incidents, whilst inadequate familiarity with equipment amounted to approximately 10% of all incidents (Cooper et al., 1978).

In the light of the current stress on anaesthetic hazards and increased interest in standardization of equipment for improvements in safety, it is appropriate for the *British Journal of Anaesthesia* to produce a Postgraduate Issue on Anaesthetic Equipment. Clearly, it it not possible in one issue to review comprehensively all the equipment which the anaesthetist uses, both to administer anaesthetics and to monitor vital physiological functions, but in keeping with the foregoing philosophy, the accent has been placed on understanding of principles and safety.

The issue commences with a historical review of the development of the anaesthetic machine, and emphasizes key developments, which have been milestones in the genesis of the modern machine; this is followed by concise accounts of the principles of breathing systems and vaporizers, and a brief account of paediatric equipment has been included, since the average anaesthetist will be only an occasional user of this equipment.

In recent years, the complexity of anaesthetic equipment has been augmented by the necessity to install scavenging systems for waste gases. This subject is worthy of separate consideration here, since it has greatly increased the potential hazards to the patient by the possibility of application of excessive sub- or supra-atmospheric pressure to his lungs.

Our final topics review two aspects related to improvements in overall safety, notably in the form of an essay on the value of warning devices and a brief review of the present state of agreement reached on standardization of anaesthetic equipment.

It is hoped that these reviews will stimulate anaesthetists to increase their understanding of equipment and seek for ways of improving design.

G. Smith
C. M. Conway

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DEVELOPMENT OF ANAESTHETIC MACHINES

P. W. THOMPSON AND D. J. WILKINSON

> '*Not always was the Kangaroo as now we do behold him, but a different Animal...*'
>
> Kipling R. (1902) *Just So Stories*

It is abundantly clear that, during the past few years, there has been a remarkable resurgence of interest in all aspects of the history of anaesthesia, and not least in that of anaesthetic apparatus. Not only academic departments of anaesthesia, but also smaller general hospitals are now admitting to some form of collection of historical anaesthetic apparatus which has been garnered by devotees, often over many years, rescuing important items from the over-enthusiastic clearance of theatre store-rooms and cupboards. One of the most notable collections in Britain is the Charles King collection owned by the Association of Anaesthetists of Great Britain and Ireland. This collection was assembled patiently over his lifetime by the instrument maker A. Charles King and has since been augmented by items from all parts of the world. It was described in detail by Thomas (1975). To anyone familiar with this work, the sheer impossibility of attempting to describe the development of the anaesthetic machine in a single article must be only too apparent. However, the writers feel that there are certain pieces of apparatus or innovative developments which stand out from the historical scene as milestones in the continuing evolution of our specialty, and which can reasonably be regarded as turning points in the equipment story. Our purpose is to highlight these and not to make any attempt to describe in detail the history of particular pieces of equipment. Many others have already given clear and detailed accounts of such history (Miller, 1941; Waters, 1946; Duncum, 1947; Jackson, 1955; Sykes, 1960/61, 1982; Rendell-Baker, 1963, 1980; Thomas, 1975; Wilkinson, 1984).

It is probably true to say that the efforts of those developing anaesthetic apparatus have been directed towards increasing safety, improving accuracy and, particularly recently, studying the ergonomic aspects of machine design and adding to sophistication. While designers would, no doubt, claim that in every instance the achievement of the second and third aims has contributed inevitably to the achievement of the first, there are many who consider the reverse to be true, since increasing complexity often engenders an increase in the opportunities for failure.

The claims of Crawford Long for primacy in the introduction of ether are now clearly recognized (Sykes, 1982); however, since he used the corner of a towel (Young, 1897), it is not unreasonable to regard Morton's draw-over apparatus as the forerunner of all (fig. 1). Simple as it was, it nevertheless incorporated some design features which have persisted until today or which could well be emulated. The ease with which it could be replaced is emphasized in the classical, albeit unproven, story of Morton's having dropped the device and broken it on his way to the public demonstration at the Massachusetts General Hospital on October 16, 1846. Even in this apparatus, the most basic principle of vaporization was appreciated and incorporated. Bigelow (1846) described "sponges to enlarge the evaporating surface" and there was little resistance to respiration with the wide-bore inspiratory tube. The evidence cited by Thomas (1975) also makes clear how rapidly improvements could be made, inasmuch as the model used on October 16 had no valves, whilst that used in the second operation on October 17 and described in Bigelow's paper did incorporate valves in the brass mouthpiece. A multiplicity of vaporizers was rapidly produced and the records of the Westminster Medical Society (later the Medical Society of London) show that there were frequent meetings at which these were demonstrated by their proud inventors.

True efficiency and accuracy in these early devices were not deemed important. Surgeons,

---

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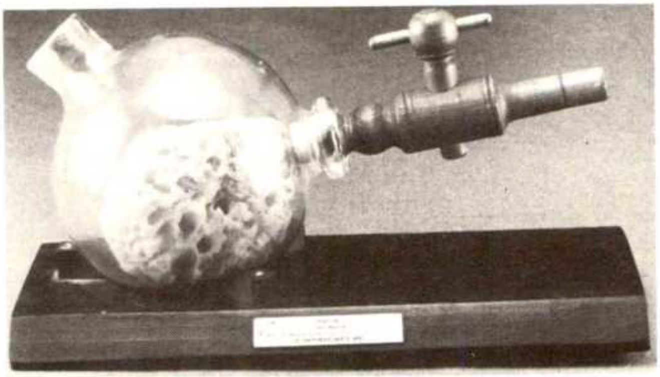

FIG. 1. Morton's ether inhaler.

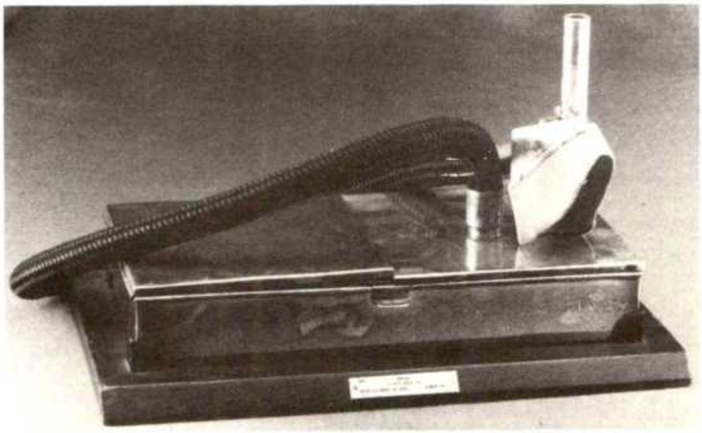

FIG. 2. Snow's ether inhaler.

used to operating on conscious, restrained patients were, by today's standards, unbelievably rapid in their work. Patients needed to be anaesthetized for only a short period to permit surgery to be completed. With the advent of effective anaesthesia, surgeons became more adventurous in the type of operation they were willing to undertake and also began to take greater care in minimizing the trauma suffered by their patients. Operations began to take longer and longer and more efficient apparatus was needed to cope with this.

Snow's ether inhaler (fig. 2) was described in his book on ether (1847) and demonstrates the thought and knowledge which he applied. He appreciated, even in those early days, the need for wide-bore tubing, adequate exposure of the ether area, and warming of the vaporizing chamber. Moreover, he specified most carefully the height of the screw-on air inlet tube required to combine minimum resistance to the ingress of air with effective "prevention of a trifling loss of ether which would arise from evaporation of it into the apartment".

Snow also developed, in 1848, a chloroform inhaler (Duncum, 1947), but his famous administration of chloroform to Queen Victoria on April 7, 1853 was described in his diary "I commenced to give a little chloroform with each pain by pouring about 15 minims by measure on a folded handkerchief". On April 14, 1857 at the birth of Princess Beatrice, he "poured about 10 minims of chloroform on a handkerchief folded in a conical shape for each pain". It may be noted that he also recorded that "Prince Albert had previously administered a very little chloroform on a handkerchief" (Snow, 1853, 1857). This, however, was not full surgical anaesthesia, and Snow was utilizing the analgesic phase of chloroform inhalation to provide obstetric analgesia.

In the following years there were two main lines

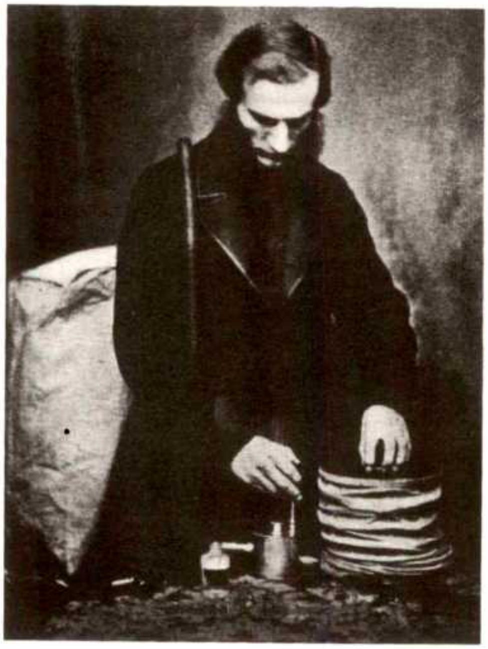

FIG. 3. Clover's chloroform bag.

of development. One was concerned with regulating the amount of vapour inhaled and the other was the utilization of nitrous oxide and oxygen as these became available stored in cylinders. In 1862 Clover showed his chloroform apparatus (fig. 3) at the International Exhibition in London. This apparatus enabled the administration of a known concentration of chloroform vapour in air. It was made to a specification drawn up by Clover himself—a specification which was detailed in every respect as to the construction, the nature of the layers of the bag, its volume and the stroke volume of the bellows used to inflate the bag. Unfortunately, one manufacturer produced a Clover bag which did not match this specification, in that the capacity of the main reservoir bag was less than that suggested by Clover. In fact it held not 11 000 but 8 400 cubic inches. It was also found subsequently that prolonged storage had made the bellows stiff and they did not deliver the supposed 1 000 cubic inches per stroke. This meant that the concentration of chloroform vapour within the reservoir bag was considerably greater than was intended and this resulted, on May 15, 1873, in the death of one Thomas Breton, an inmate of Broadmoor Asylum for the criminally insane. Subsequently, Clover himself examined the bag with Mr Coxeter and the defects they found were reported immediately to the *Lancet* (Orange, 1873). Perhaps it was this event which can be regarded as the first appreciation of the necessity for accuracy and conformation with standard specifications which has become so much a part of the anaesthetic equipment industry today.

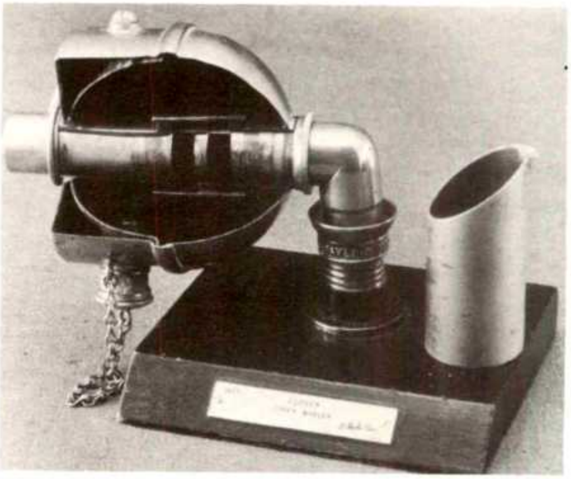

FIG. 4. Clover's portable regulating ether inhaler.

In 1877, Clover described his portable regulating ether inhaler (fig. 4). Rotation of the control determined the proportion of each breath which was diverted into the ether chamber. This was the first attempt to quantify a vaporizer and, although the apparatus was not calibrated in percentages, it was a considerable step forward. It may also be noted that the diameter of the face-mask fitting was 22 mm—a standard which is accepted internationally today!

The Clover type of ether inhaler remained popular in the U.K. for many years. Hewitt improved on Clover's ether inhaler with his wide-bore version in 1901; this reduced the resistance to respiration and allowed easier manipulation of the control, and the face-mask was screwed to the reservoir—a forerunner of the anti-disconnect devices which are gaining increasing favour today. It was as late as 1908 that Ombrédanne published the paper on his ether inhaler (fig. 5). He paid particular attention to respiratory resistances and to the incorporation of a stepped air inlet. This vaporizer became more widely accepted on the European mainland than either the Clover or Hewitt models.

Although nitrous oxide was the agent used by Horace Wells in 1845, its widespread use was limited considerably by the need to maintain a

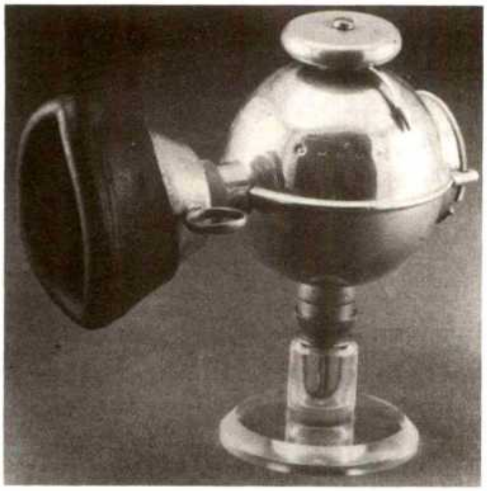

FIG. 5. Ombrédanne's ether inhaler.

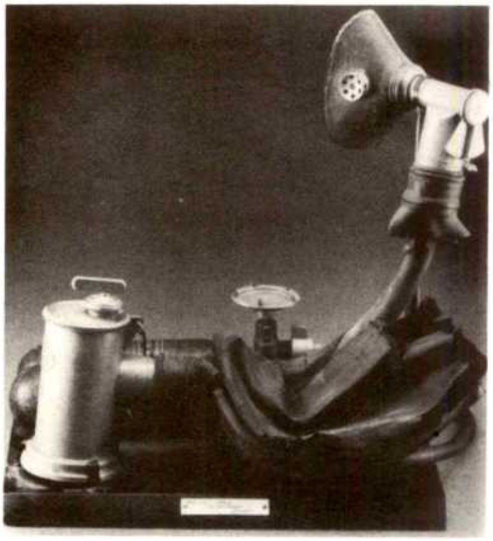

FIG. 6. Clover's nitrous oxide/ether apparatus.

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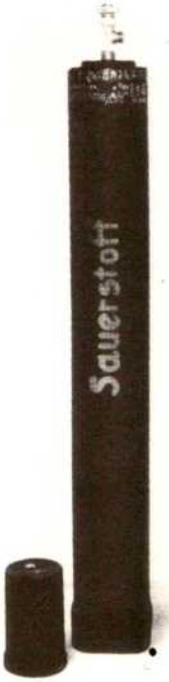

FIG. 7. Oxygen bottle from 1885.

generator for the gas and some form of storage. The entire story of nitrous oxide anaesthesia has been comprehensively reviewed by Smith (1982). In the period 1860–1870, a wide variety of designs of "gasometer" was marketed. The firms of Barth and Coxeter & Son were manufacturing nitrous oxide in 1868 and supplying it in iron bottles; in 1870 they succeeded in liquefying the gas. However, the compressed gas was not easy to control, although various ingenious devices such as Hele's Governor (Duncum, 1947) were introduced in the 1870s. Even so, in 1876 Clover was able to develop his nitrous oxide and ether apparatus (fig. 6). This was the first attempt to use a nitrous oxide–ether sequence. Perhaps of all historical apparatus, this particular device has failed to receive the recognition that it deserves. Anaesthesia was induced with nitrous oxide from the reservoir bag and maintained with ether drawn through the vaporizer. This greatly facilitated an otherwise prolonged ether-in-air induction and must have been more pleasant for the patient. Air was not admitted until cyanosis or jactitation occurred. Clover himself, however, never liked this apparatus and preferred his portable regulating ether inhaler which rapidly became modified with the addition of a stopcock and bag to permit sequential anaesthesia.

In the 1880s, technology succeeded in storing pure oxygen, prepared by the newly developed Lind process, in steel cylinders at high pressure. Figure 7 shows a cylinder which bears a test stamp for the year 1885. It was a prerequisite for the utilization of compressed gases stored in this way that there should be a serviceable and efficient means of controlling both the flow and pressure of the gas released. The founders of Drägerwerk, Heinrich Dräger and his son Bernhard, became involved with compressed gas engineering while it was still in its infancy. They were originally acting as agents for equipment used in connection with the compressed gas pressurization of beer barrels. Being unsatisfied with various apparatus from diverse origins and of considerable unreliability, they decided that their first step should be to develop an "excellent and efficient" pressure reducing valve. Heinrich Dräger described those already available as "very undiscriminating" and that "they were very often disappointed with performance". As a result of their thinking they developed a completely new construction. Since the manufacturers for whom they were agents declined to take up this new valve the Drägers set up in business on their own. From this Bierdruck Automat—a mechanism for the automatic control of carbon dioxide pressure in beer pumps—stemmed the effective control of compressed medical gases. This development was followed almost immediately by their production of an effective control valve for cylinders, and the combination of these two allowed an even flow of gas to be drawn from a high pressure cylinder with accuracy, regardless of whether the pressure in the cylinder was high or low. These two inventive engineers were also the first to introduce the injector to a variety of anaesthetic apparatus and ventilators. However, in Britain, anaesthetic reducing valves continued to be based on that developed originally by Beard (fig. 8) for the control of acetylene–oxygen mixtures for limelights.

In the 1890s Hewitt had also introduced, as part of a nitrous oxide and oxygen apparatus, his nitrous oxide and oxygen stop-cock, which allowed the administration of a mixture of nitrous oxide and oxygen (Hewitt, 1897). Hewitt pointed out that it was impossible to state with precision what percentage of oxygen would be delivered at any given setting. He also stressed the importance of equalizing the pressure in the oxygen and nitrous oxide reservoirs and produced a conjoined pair which shared a common septum—the forerunner of the pressure-equalizing devices which were to be so important in the development of the intermittent flow machines such as the McKesson and Walton.

No review of the development of anaesthetic apparatus can omit the work of Harcourt (1903). The place of his apparatus (fig. 9) was stressed by Wilkinson (1984). He wrote "one of the most popular of the chloroform vaporizers was that designed by Vernon Harcourt. This apparatus was

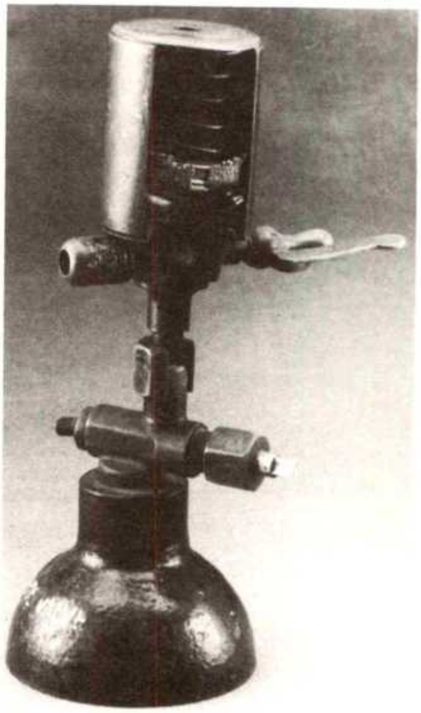

FIG. 8. Beard pressure-reducing valve.

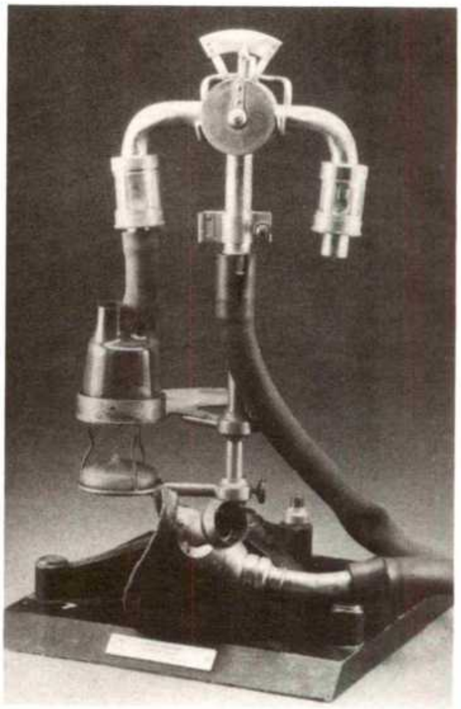

FIG. 9. Vernon Harcourt chloroform inhaler.

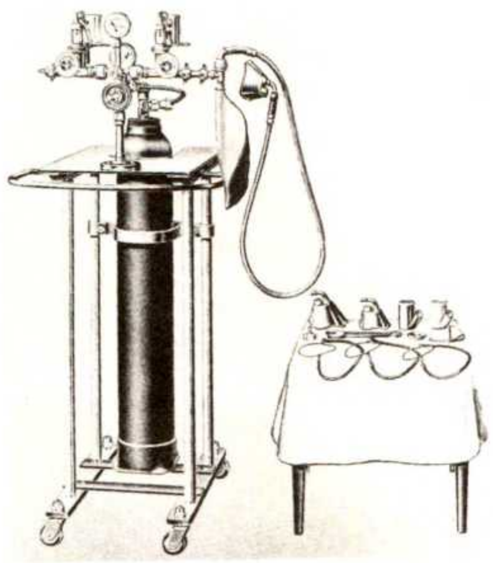

FIG. 10. Roth-Dräger mixed anaesthesia apparatus.

said to deliver not more than 2% chloroform in air regardless of the respiratory volumes. It was calibrated as accurate over a specific temperature range and incorporated a form of thermometer in the vaporizing chamber. This consisted of two special beads which floated or sank depending on the temperature of the liquid chloroform; the glass bottle containing the liquid could be heated on some models by the use of a candle to achieve the correct working temperature—heating must have increased the levels of phosgene delivered considerably! However, the apparatus demonstrates many sophisticated design points that would be incorporated in later equipment notably its air bypass, temperature compensation, and compensation for the fall in chloroform levels by tapering the glass bottle in which it was held."

In summary, therefore, just after the end of the 19th century a point had been reached at which it was possible to give relatively uncontrolled nitrous oxide and oxygen mixtures (the precise proportion of oxygen in which was not known for certain), together with a volatile agent.

In 1902 the Drägers produced their first anaesthetic apparatus in conjunction with Dr Roth of the Lubeck General Hospital (fig. 10). This incorporated an oxygen cylinder and reducing valve, the oxygen being used to operate two injectors which sucked ether or chloroform, or both, from separate bottles for evaporation, the number of drops being carefully regulated. However, what was still missing was an accurate control and means of measuring gas flow. Cotton and Boothby (1912) were the first to use the "bubble bottle" for visible gas measurements in anaesthesia. It was this development which lead to the apparatuses devised by Gwathmey, Marshall, Boyle and others. As Smith (1982) noted in his book, "Boothby and Cotton had made worthwhile advances in the design of apparatus. Knowledge of the amount of each gas being used was 'obtained by passing the gases through water into a mixing chamber; the rate of the bubbling of the gas through the water gives a very accurate index of the percentages of the two gases as administered to the patient'". Undoubtedly, this was a fundamental step which preceded by a very few years the development of the Gwathmey and Boyle apparatuses. Accurate though these flowmeters were compared with previous methods, they must have been very difficult to read. Relatively low gas flows produced considerable turbulence and made accurate readings difficult. They did, however, have the advantage of humidifying the inspired gases. Rendell-Baker (1963) pointed out that "Rotameters were first used in industry in Great Britain before the first world war and were also employed to measure gas flows by manufacturers of medical gases. Their use in anaesthesia was later explored by McCardie of Birmingham and Magill in London, but it was not until 1937 that Rotameters became available commercially for anaesthesia after their modification had again been suggested by Salt". Rendell-Baker also noted that Neu in 1910 produced an experimental nitrous oxide–oxygen apparatus with Rotameters made by Deutsche Rotawerke of Aachen which were identical in principle with those of the present day. He suggested that their large size and high cost were the reasons for the lack of interest shown by the rest of the world, and that the fact that nitrous oxide was imported into Germany was a further factor retarding the development of this early and accurate method.

The contributions of Gwathmey to anaesthesia were monumental (Thomas, 1975). One of the first physicians in the United States to confine himself entirely to anaesthetic practice, he reported on 20000 successful cases of the use of rectal ether in midwifery, produced a comprehensive text book (Gwathmey, 1914), and was largely instrumental in the development of the American Society of Anesthesiologists. During the 1914–18 war he and Boyle of St Bartholomew's Hospital in London renewed an earlier acquaintance. Gwathmey had introduced his apparatus in 1912 using the same type of flowmeter as Cotton and Boothby. No pressure reduction of the compressed gases was included, but stress was laid on warming the inspired gases, and the use of a "sliding cuff" inspiratory and expiratory valve which allowed regulation of degree of rebreathing. Marshall, also working in France during the war, developed an apparatus for giving gas, oxygen and ether with wet flowmeters. A prototype of his apparatus was produced by Coxeter and this became a standard model in the Royal Army Medical Corps. However, before Marshall had published an account of his apparatus (1920), Boyle had described his apparatus (1917, 1919), which was purely an English modification of Gwathmey's design. Thus, as Thomas said, "the name of Boyle became forever associated with this type of anaesthetic apparatus". As Hadfield (1950) said, "Boyle and his contemporaries played an important part in bridging the gap between earlier methods and those which were developed into the techniques of today". The situation was summed up by Thomas "...Gwathmey and Marshall developed the use of nitrous oxide with oxygen and produced a new method of gauging the gas flows. This was the idea which was then taken up by Boyle". The steady development of this type of apparatus from 1917 (fig. 11) to the present day is one of steady refinement. In his 1927 model, a flowmeter for carbon dioxide was included, the volatile controls were of the lever type and the familiar back-bar made its first appearance. The plunger of the vaporizer appeared in the 1930 model (fig. 12), and in the 1933 model Coxeter dry bobbin flowmeters were incorporated.

The early development of vaporizers has already been described under such headings as Clover, Harcourt and the Boyle apparatus. Over the past 20 years the steady development of a wide range of accurate temperature-compensated vaporizers such as the Fluotec, Dräger "Vapor", and "Abingdon" suitable for use with low flows of fresh gas has taken place. The development of these vaporizers has been described by Wilkinson (1984).

Mention should be made of the development of closed breathing systems and carbon dioxide absorption. This is indelibly and inextricably linked with the name of Waters of Madison. However, the development of carbon dioxide absorption was originally undertaken to meet the requirements of the mining industry. On June 15, 1856, Schwann breathed from his newly-invented mine rescue apparatus, which incorporated an absorption chamber for caustic soda, for 1 h 45 min. Again, the Drägers played a key role in the development of subsequent apparatus and produ-

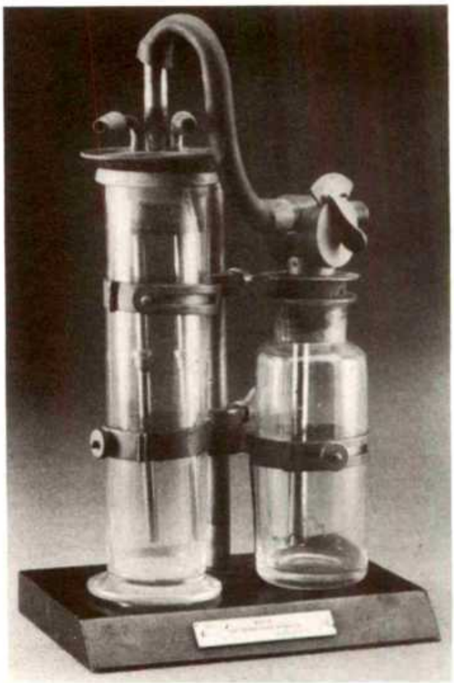
FIG. 11. Boyle's apparatus (1917).

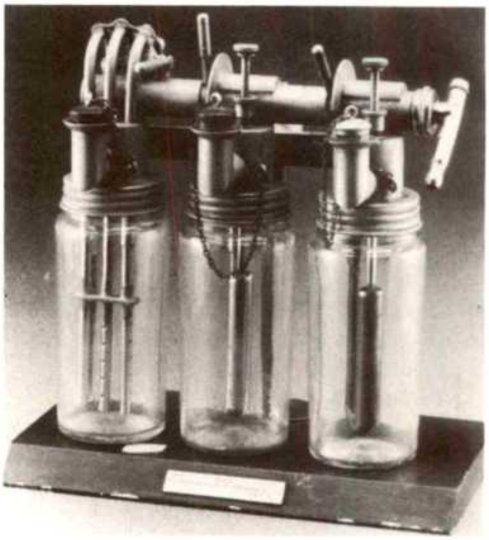
FIG. 12. Boyle's apparatus (1930).

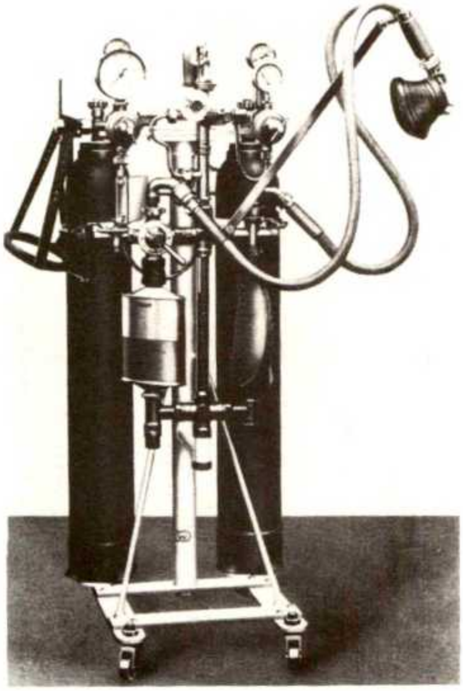

FIG. 13. Dräger nitrous oxide anaesthesia apparatus model A.

ced a series of commercial models in the early 1900s. In 1924 they incorporated a Dräger absorption canister in an entirely satisfactory anaesthetic apparatus—the Dräger Sauerstoff–Lachgas–Narkose Apparatus modell A, introduced by Sudech and Schmidt in the University Hospital, Ependorff (fig. 13). The intentions were to economize in the cost of anaesthetic agents and to reduce the explosion hazard—the latter aim not being wholly achieved!

Meanwhile, in the U.S.A., Jackson had developed an effective carbon dioxide absorption apparatus with the intention of economizing in nitrous oxide and oxygen. His "very first machine in which the closed system of anaesthesia was ever used" was produced in 1914. Although the apparatus was constructed of such homely items as cake tins and bathing caps, he stressed the importance of reducing deadspace to a minimum and making the tubing a full 1 inch in diameter so as to give the patient an adequate airway. This apparatus was intended particularly for the dog; for man he had an opening of 3 inches in diameter between the face-mask and the immediately adjoining breathing bag. The collaboration between Waters and Jackson began in 1920, Jackson being happy to have Waters develop his ideas for, as a pharmacologist, he lacked access to clinical studies. The work culminated in the introduction by Waters of his to-and-fro absorption apparatus in 1924, but this did not achieve widespread popularity until the clinical introduction of cyclopropane in 1930. The circle absorption system developed by Sword with the help of Foregger was introduced in 1930.

In all too limited a space, an attempt has been made to outline in the barest detail the development of the modern anaesthetic apparatus. No mention has been made of such equipment as the open mask, the intermittent flow machine, the incorporation of lung ventilators in the apparatus, or the increasing inclusion of warning and monitoring devices. The situation is constantly changing. It may well be that by the time this article is read the appearance of a revolutionary "third generation" of anaesthetic machine may have been reported—one which applies a truly up-to-date refinement to, *inter alia*, an aspect to which particular attention has been paid here: the increasing accuracy of delivered mixtures. There have been many changes in the development of anaesthetic apparatus since 1846. Essentially, however, little has changed since the 1930s when Boyle refined his original apparatus. Unfortunately, most equipment is now the province of the multi-national corporations who produce apparatus based on ISO requirements, published or in draft (Thompson, 1983), and not those of the anaesthetist. Most anaesthetists today lack the facilities, aptitude or time to manufacture their own equipment and are thus increasingly dependent on what is made for them. Instrument manufacturers have large sums of money invested in tooling and factories and are often unwilling to make major changes in design. It is surely time for a reappraisal of this situation. It is time also for the anaesthetist to begin influencing anaesthetic apparatus manufacturers again to ensure that the evolution of our specialty continues to keep pace with the developments in engineering and bio-mechanics that are taking place today.

ACKNOWLEDGEMENTS

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ANAESTHETIC BREATHING SYSTEMS

C. M. CONWAY

A patient receiving an inhalation anaesthetic is most commonly connected to an anaesthetic machine by some form of breathing system. Whilst modern anaesthetic machines are designed to deliver gas mixtures of accurately known composition and flow, the chosen breathing system can greatly influence the composition of the gas mixture breathed by the subject. This article examines the way in which commonly used breathing systems function and suggests safe ways in which they may be used.

Anaesthetic breathing systems may be used in different ways for different purposes. Under some circumstances, it is correct to use a breathing system in a manner that ensures that the inspired mixture delivered to a patient is identical in composition to the fresh gas delivered from the anaesthetic machine. In other circumstances, one may use the differences which a breathing system can produce between the composition of gas delivered from the anaesthetic machine and the inspired gas mixture in order to optimize either the course of anaesthetic gas delivery or the conditions for pulmonary gas exchange.

CLASSIFICATION

A number of descriptive terms are traditionally associated with the definition of breathing systems—open, closed, semi-open and semi-closed. Many different classifications of the various breathing systems have been suggested on the basis of these four terms. As "open" and "closed" are defined in different ways by different authors, and as any difference between the terms semi-open and semi-closed cannot be defended on semantic grounds, classifications of breathing systems based on these traditional terms create more confusion than clarification. A further complication is that the categorization of a particular breathing system as open or closed can be changed by minor modifications in the way that it is used, so that some systems can easily be used both as open and closed systems.

A more rational approach to the classification of breathing systems is to define them in terms of their geometry. This approach allows allocation into two broad classes—systems which do not contain the means to absorb carbon dioxide and those equipped with carbon dioxide absorption equipment. The majority of systems allocated to the first class may be named by using the widely accepted Mapleson classification (Mapleson, 1954, 1958; Willis, Pender and Mapleson, 1975) illustrated in figure 1. These may be classified as rebreathing systems, rebreathing here referring to the potential rebreathing of expired carbon dioxide-containing gas. The only absorption system in common use is the circle system. This article considers the rebreathing and absorption systems. It does not deal with the breathing systems specifically designed for use with ventilators. These are almost invariably designed to produce non-rebreathing conditions by separating inspired and expired gases using mechanically operated valves. In addition, this article does not deal with systems which use a simple patient-activated non-rebreathing valve. The point of interest in such systems is not how they work but whether or not the non-rebreathing valve does in practice separate inspired and expired gases.

REBREATHING

With simple rebreathing systems not using carbon dioxide absorption, it is always possible for the subject to re-inspire some of his previously expired gas. A common method of defining the way in which these systems should be used is to describe the fresh gas flow needed to prevent such rebreathing. Rebreathing has no physiological consequences unless the rebreathed gas has a carbon dioxide-containing component which

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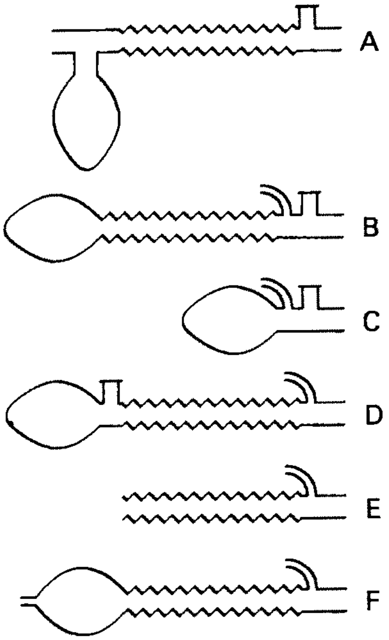

FIG. 1. The six Mapleson rebreathing systems. Modified from Willis, Pender and Mapleson (1975).

enters the subject's alveolar space. It is possible with some breathing systems for the subject to "rebreathe" expired deadspace gas, which may have the same composition (other than the presence of water vapour) as fresh gas. Other systems have the capacity to store fresh gas unmixed with expired gas, and "rebreathing" of such gas is of no consequence. Expired alveolar gas rebreathed into the subject's deadspace is also of little consequence to the subject.

The effect of rebreathing expired alveolar gas in conscious subjects is not commonly for alveolar and arterial carbon dioxide tensions to increase, but rather for ventilation to increase in order to maintain a normal or near normal alveolar carbon dioxide concentration. This is also the response in the majority of lightly anaesthetized spontaneously breathing subjects (Byrick, 1980). Deeper levels of anaesthesia obtund a subject's ability to respond to a carbon dioxide load and can result in an increase in Pa_{CO_2} without an increase in ventilation. In spontaneously breathing anaesthetized subjects the presence or absence of rebreathing cannot be detected merely by measuring arterial carbon dioxide tension. In addition, it cannot always be recognized easily by monitoring inspired carbon dioxide concentration, for this may be increased during parts of inspiration and decrease to zero during other parts of the inspiratory period.

If rebreathing is to be avoided in spontaneously breathing subjects, then the necessary fresh gas flow should be defined as that flow which prevents both ventilation and arterial carbon dioxide tension changing from the resting anaesthetized state. During controlled ventilation, as ventilation is under the control of the operator, it is essential to define both the fresh gas flow and the ventilation used to produce any given value of arterial carbon dioxide tension.

During spontaneous ventilation, rebreathing of carbon dioxide containing gas is always to be avoided. Of necessity, such gas will contain less oxygen and less anaesthetic than fresh gas. Neither of the potential respiratory consequences of rebreathing—an increased ventilation or an increased arterial $P\text{CO}_2$—can be considered desirable attributes of a well conducted anaesthetic. Rebreathing is of less consequence during controlled ventilation, for the administrator can control the $P\text{CO}_2$ by increasing ventilation. There is some advocacy for allowing rebreathing during controlled ventilation with simple breathing systems in order to obtain a state of alveolar hyperventilation with normocapnia. Rebreathing of expired alveolar gas during the use of a circle system is of course a fundamental consequence of the use of such a system and can only be prevented by the use of high fresh gas flows.

REBREATHING SYSTEMS

Mapleson A (Magill) system

The Magill attachment differs from the other systems shown in figure 1 in that fresh gas flow does not enter the system close to the subject, but at the remote end of the system. Because of this, and because the expiratory valve is at the subject end of the system, expired alveolar gas tends to be vented selectively from the A system during spontaneous breathing. In the early stages of expiration with this system, expired gases pass down the corrugated tubing whilst fresh gas entering the system flows into the reservoir bag. As the system fills, pressure in the system increases, and eventually the expiratory valve opens. For the remainder of expiration, expired gas escapes from the valve. At the same time, fresh gas flowing down the tubing pushes before it the expired gas deposited in the system early in expiration. Theoretically, a fresh gas flow equal to the subject's alveolar ventilation should allow at each breath the expulsion of all expired alveolar gas from the system with retention of deadspace gas. In both conscious volunteers and lightly anaesthetized subjects, the A system has been shown to function without evidence of rebreathing with fresh gas flows close to the subjects' predicted alveolar ventilation: 60–70% of minute volume (Kain and Nunn, 1968; Norman, Adams and Sykes, 1968; Conway et al., 1976). Because it is difficult to predict alveolar ventilation with great accuracy, and as alveolar ventilation may vary from breath to breath, it is wiser in practice to use a slightly higher flow than the theoretical minimum, say 80–90% of minute volume.

The A system loses all its virtues of economy when used for controlled ventilation. Under these conditions, as the expiratory valve opens during inspiration, the tendency is for alveolar gas to be retained within the system. During inspiration a mixture of fresh and expired gas enters the subject's lungs and leaves the system through the valve. The composition of the inspired gas mixture is critically dependent upon the imposed respiratory pattern. Normocapnia can be obtained under these conditions by using increased fresh gas flow and ventilation. Unless means are available to monitor end-tidal carbon dioxide concentrations, the Magill attachment should not be used during controlled ventilation.

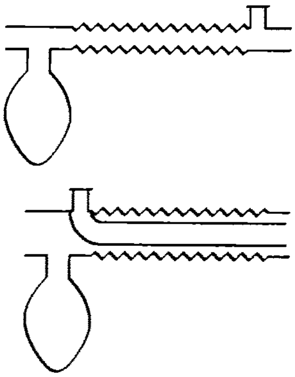

FIG. 2. The Magill (Mapleson A) system and (below) the Lack coaxial A system.

The Lack system (Lack, 1976) is a coaxial version of the A system (fig. 2) in which the expiratory valve is sited at the machine end of the system and is connected to the subject by the inner coaxial tube. Early versions of this system suffered from two defects (Barnes et al., 1976). Because these versions were constructed of a conventional length of corrugated tubing with a narrower inner tube, the resistance of the system was unacceptably high. More interestingly, the presence of the inner tube resulted in a reduction of the capacity of the limb of the system connecting the subject to the reservoir bag from a normal volume of some 500 ml down to approximately half this volume. Early in expiration, before the expiratory valve opens, expired gas is stored in this limb. With these early versions of the Lack system it was possible for carbon dioxide containing expired gas to traverse this limb and enter the reservoir bag. Expired gas in the reservoir bag could not be flushed from the system later in expiration, but formed part of the next inspirate. This could only be prevented from occurring by using a fresh gas flow considerably greater than that needed for the conventional A system, so as to ensure opening of the expiratory valve early in expiration. These disadvantages of the earlier Lack system have been overcome in the current versions by using outer tubing of a wider diameter and of a greater length than the conventional corrugated tubing, and by increasing the diameter of the inner tube. Some disagreement surrounds the function of the Lack system *vis-à-vis* the conventional A system. Barnes, Conway and Purcell (1980) have claimed that the Lack system is somewhat less efficient than the non-coaxial A system, whilst Nott, Walters and Norman (1977) in their trials have shown the two systems to have an equal efficiency. The differences between these two claims have little import in clinical practice, for as noted above it is wiser to use a fresh gas flow somewhat above the basal value with the A system. Humphrey (1982) has claimed that the Lack system is considerably superior to the conventional A system, the latter requiring higher fresh gas flows to ensure efficient performance. It should be noted in assessing this claim that, for any breathing system not equipped with means for carbon dioxide absorption, the lowest possible fresh gas flow needed to maintain an unchanged $P\text{CO}_2$ and ventilation is equal to the subject's alveolar ventilation for, assuming alveolar gas alone to be vented from the system, this level of fresh gas flow is needed to remove the carbon dioxide output without an increase in alveolar carbon dioxide tension. Many workers (Kain and Nunn, 1968; Norman, Adams and Sykes, 1968; Conway et al., 1976) have shown the conventional A system to function efficiently at this fresh gas flow. As, in the work reported by Humphrey (1982), flows much larger than alveolar ventilation were needed for the conventional A system, one should regard their findings as demonstrating a methodological difference in experimental technique rather than any large advantage of the Lack system.

The B and C systems

These are the least commonly used of the simple rebreathing systems. The B system differs from the C system only in having a length of corrugated tubing interposed between the reservoir bag and site of entry of fresh gas. The C system is occasionally used during induction of anaesthesia, and versions of this system are often available outside operating theatre circumstances for resuscitation purposes. The B system is little used in clinical practice. These systems have a blind limb, and for their effective use during spontaneous breathing it is essential that expired alveolar gas be prevented from entering this limb. Mapleson (1954) recommended fresh gas flows of the order of 2.5 times minute volume for use with these systems. It is possible to show that, in theory, these systems function effectively at lower fresh gas flows. If fresh gas flow is such that the expiratory valve opens during expiration when deadspace gas alone has entered the system, and if thereafter all fresh and expired gas entering the system during expiration is expelled through the valve, then expelled gas consists of all expired alveolar gas and some fresh gas. Depending on the deadspace to tidal volume ratio and the characteristics of expiratory flow, this condition requires a fresh gas flow of between 0.8 and 1.2 times the minute volume. In limited and unreported studies carried out in the author's laboratory, in which trained volunteers breathed from a B system supplied with a non-anaesthetic fresh gas, it was possible in a few volunteers to maintain normocapnia and an unchanged ventilation with fresh gas flows in the order of the subjects' minute volumes. The system under these conditions is highly unstable. A slightly increased tidal volume results in carbon dioxide-containing gas entering the tubing and reservoir bag and leads to progressive rebreathing. Used during controlled ventilation, the B and C systems have an efficiency only slightly better than that of the A system. Under these conditions a mixture of fresh and expired gases forms in the reservoir bag during expiration and this mixture constitutes a major part of the succeeding inspirate. Normocapnia can be produced by using fresh gas flows and ventilation both of about twice resting minute volume. Because the composition of inspired gas is greatly influenced by the pattern of imposed ventilation, these systems, like the A system, have a variable performance during controlled ventilation. There are therefore no reasons for advocating the use of the B or C system during either spontaneous or controlled ventilation.

The D, E and F systems—T-pieces

These three systems have an identical geometry at their subject ends, and have a near identical performance. Gas disposition at the T portion of these systems determines their function. Whether at the far end of the system gas escapes through a valve, open-ended tube or double-ended bag, little affects their mode of action. In all of these systems one can ensure, during either spontaneous or controlled ventilation, that fresh gas alone forms the inspirate if fresh gas flow equals or exceeds peak inspiratory flow rate, for under these conditions fresh gas flow always satisfies inspiratory requirements. This requires a fresh gas flow of some three times resting minute volume. It is possible to prevent rebreathing of alveolar gas at fresh gas flows much lower than these values. The theory governing the behaviour of T-pieces at low fresh gas flows has been described by Onchi, Hayashi and Ueyama (1957) and by Willis, Pender and Mapleson (1975). The factors influencing behaviour under these conditions are illustrated in figure 3. Figure 3A shows a representative inspiratory flow curve and a superimposed fresh gas flow (*V*F). Fresh gas flow is below peak inspiratory flow. Areas on this flow–time graph represent volumes. The total area under the flow

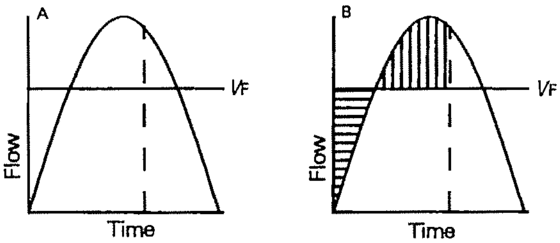

FIG. 3. Representative inspiratory waveforms to demonstrate inspired gas composition during the use of T-piece systems. The lines marked *V*F represent fresh gas flow and the vertical interrupted lines show the division between the alveolar and deadspace components of inspired gas. For further explanation see text.

curve represents tidal volume. The dotted vertical line separates inspired gas destined to enter the alveolar space (to the left of this line) from that gas which enters the deadspace and thus does not take part in gas exchange. Early and late in inspiration, fresh gas flow exceeds inspiratory flow, and the inspirate at these times consists only of fresh gas. In the mid portion of inspiration when inspiratory flow exceeds fresh gas flow, the inspirate consists of all fresh gas entering the system at that time plus some gas previously deposited in the subject end of the tubing of the system. In figure 3B, the vertically hatched area above the fresh gas flow line denotes this volume of "rebreathed" gas which enters the alveolar space and takes part in gas exchange. The effects of this rebreathing depend on the composition of the "rebreathed" gas.

Early in inspiration, fresh gas enters the system in excess of inspiratory requirements. The horizontally shaded area on figure 3B shows this volume of excess fresh gas, which enters the subject end of the T system. If this bolus of fresh gas remains unmixed with expired gas, and if its volume equals the volume of gas that is "rebreathed" into the alveolar space, then the alveolar inspirate consists of fresh gas alone. This condition is satisfied when fresh gas flow is of the order of twice minute volume. The exact figure depends on the characteristics of inspiratory flow, deadspace–tidal volume ratio and the relative durations of inspiration and expiration. Willis, Pender and Mapleson (1975) have shown T-pieces to function according to this theory in conscious volunteers. Conway, Seeley and Barnes (1977) have shown that, in conventional T-piece systems, there is little tendency for longitudinal mixing of gases to occur along the reservoir limb of a T-piece, and thus the fresh gas excess entering the system early in inspiration can be stored in the system unmixed with other gases. The economy of a T-piece system is improved if there is an end-expiratory pause, for under these conditions there is a greater reservoir of fresh gas available to satisfy any later inspiratory requirements.

Lack of longitudinal mixing of gases along the limb of a T-piece only occurs if ventilation is quiet and regular. During controlled ventilation, as peak ventilatory flows tend to be higher and reversal of flow more abrupt than during quiet spontaneous breathing, there is a tendency for fresh and expired gas entering the reservoir limb of a T-piece to form a fairly uniform mixture. If fresh gas flow is less than peak inspiratory flow, the inspirate always has an alveolar component. Alveolar carbon dioxide concentration depends upon the magnitudes of fresh gas flow and ventilation and is influenced by the characteristics of inspiratory flow. Figure 4 shows the $P\text{CO}_2$ values that occur, in theory, at various values of fresh gas flow and ventilation. It has been assumed here that inspiratory flow is square-wave in character and that the expiratory phase lasts twice as long as the inspiratory phase. It will be seen that, to obtain any desired $P\text{CO}_2$ value, there are an infinite number of combinations of fresh gas flow and ventilation that may be used. When fresh gas flow is high, $P\text{CO}_2$ is virtually independent of fresh gas flow, but greatly dependent upon the ventilation. The converse applies when a high level of ventilation is used.

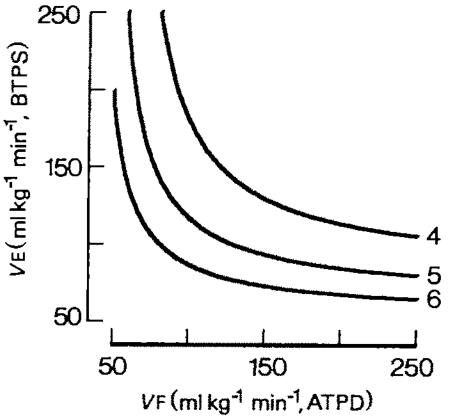

FIG. 4. Curves to show the interrelationships of $P\text{CO}_2$, fresh gas flow and ventilation when controlled ventilation is carried out using a T-piece system. The three curves are carbon dioxide isopleths at $P\text{CO}_2$ values of 4, 5 and 6 kPa.

Coaxial T-piece systems

Conventional T-piece systems have been widely used for many years during paediatric anaesthesia. Their widespread use in adults followed the description by Bain and Spoerel (1972, 1973) of a coaxial T-piece system. Coaxial versions of the D, E and F systems can be used (fig. 5). The outer tubing of commercially available versions of the Bain system is narrower (22 mm) and longer (1.8 m) than conventional corrugated tubing. The major use advocated for the Bain system is for controlled ventilation. A convenient way of doing this is to connect the outlet of a ventilator to the reservoir bag mount of the Bain system by means of a 1- or 2-m length of corrugated tubing (Adams, 1976).

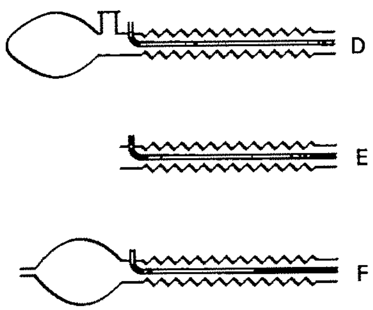

FIG. 5. Coaxial T-piece arrangements.

Used for controlled ventilation, fresh gas flows to the Bain system of 70 ml kg^{-1} min^{-1} (in adults) have been recommended (Bain and Spoerel, 1973; Henville and Adams, 1976) with ventilation of at least 150 ml kg^{-1} min^{-1}. The performance of coaxial systems during controlled ventilation should differ in no way from that of conventional T-piece systems, and figure 4 should apply to these systems. It may be seen from this figure that the co-ordinate point for these flows lies towards the flat portion of the normocapnic isopleth, where $P\mathrm{CO}_2$ is little dependent on ventilation and greatly dependent on fresh gas flow. Conway (1982) has recommended a somewhat higher fresh gas flow (100 ml kg^{-1} min^{-1}) and a lower value of ventilation (120 ml kg^{-1} min^{-1}) so that the co-ordinate point falls closer to the elbow of the normocapnic isopleth. It should be noted that the above values of flow and ventilation and the data of figure 4 apply to adults and not to children. This is because of the higher and more variable relationship between carbon dioxide output and body weight in infants.

Use of a T-piece for controlled ventilation almost invariably results in the subject receiving a carbon dioxide load, the effects of which on $P\mathrm{CO}_2$ are overcome by a degree of hyperventilation. This may be acceptable when manual ventilation is considered desirable (as in the neonate). It is possible to advance theoretical reasons why hyperventilation under normocapnic conditions may improve the distribution of ventilation, and thus be a desirable technique. There is little evidence that any advantages accrue to this approach in normal man, and it is certainly not the method commonly used to ventilate non-anaesthetized subjects, for instance, during intensive therapy. It is more logical (but often less convenient and expedient) to connect a subject directly to a lung ventilator rather than interpose between ventilator and subject a device which acts as a mixing chamber.

Although it has been recommended that, when the Bain system is used in spontaneously breathing subjects, satisfactory conditions can be obtained with fresh gas flows of 70–100 ml kg^{-1} min^{-1} (Bain and Spoerel, 1972; Spoerel, Aitken and Bain, 1978), other workers have found larger fresh gas flows to be needed. Whilst coaxial and non-coaxial T-pieces have a closely similar performance during controlled ventilation, they differ markedly when used in spontaneously breathing subjects. In conscious volunteers Conway, Seeley and Barnes (1977) found a fresh gas flow to a coaxial D system of three times minute volume was needed to prevent rebreathing. Byrick (1980) found, in anaesthetized patients breathing from a Bain system supplied with a fresh gas flow of 100 ml kg^{-1} min^{-1}, that in two-thirds of his subjects normocapnia was present but ventilation had increased by some 50%, and the remaining patients showed increases in both ventilation and $P\mathrm{CO}_2$. Nott, Walters and Norman (1977) and Humphrey (1982) have also shown that large fresh gas flows are required for the proper working of the Bain system in spontaneously breathing anaesthetized subjects. The reason for the need during spontaneous breathing for much higher flows in coaxial than in conventional T-piece systems appears to be that the entry of fresh gas parallel to the reservoir tube and directed at the subject's mouth results in considerable turbulence within the system which promotes gas mixing in the reservoir tube. This tube cannot then store fresh gas unmixed with expired gas and, to prevent rebreathing of alveolar gas, fresh gas flows in the order of peak inspiratory flow are required.

Combined systems

A number of systems which combine the A system and a T-piece (usually the D system) have been described (Waters, 1961; Manicom and Schoonbee, 1976; Miller, 1979; Humphrey, 1983). These systems have often used ingenious devices to switch between the A system (for spontaneous breathing) and the T-system (for controlled ventilation). Some of these systems have been shown to function adequately in either mode. The major disadvantage of such systems is that they require manipulation of one or more valves or taps, and malposition with dangerous malfunction can occur (Newton and Cundy, 1983). Furthermore, these systems add a not inconsiderable degree of complexity to otherwise simple breathing systems.

CIRCLE SYSTEMS

Whilst the to-and-fro method of carbon dioxide absorption introduced by Waters (1924, 1926) was widely used for many years, the inconvenience of this apparatus, the problems of increasing dead-space as the absorbant became exhausted and the dangers of excessive heat production and soda-lime dust inhalation have led to its virtual abandonment and its replacement by the circle system with unidirectional valves. In worldwide terms, the circle system is probably the most commonly used breathing system.

The performance of a circle system greatly depends upon the fresh gas flow supplied to the system. Most commonly, fresh gas flows of the order of 4–8 litre min^{-1} are used. With such flows, inspired gas differs but little in composition from fresh gas. There has been a recent resurgence of interest in the use of circle systems with flows close to basal values. This interest has been stimulated in part in the hope of reducing atmospheric pollution and in part by the increasing availability of devices to monitor gas composition in the system.

There are a number of way in which the various components of a circle system can be assembled. The geometry of the system can influence its behaviour, and these influences of geometry have been studied comprehensively by Eger and his associates (Eger and Ethans, 1968; Eger, 1974; Harper and Eger, 1976). The geometry of a circle system only influences its performance if gas within the system is largely unmixed. Schoonbee and Conway (1981) have shown that changes in the character of ventilation can greatly vary the degree of gas mixing in a circle system, and these variations can outshadow the influences of circle system geometry. The effects of geometry and of ventilation upon circle system performance are of importance when high fresh gas flows are used. With fresh gas flows close to basal values, there is a tendency for most gas within the system to be mixed uniformly, and variations in geometry or the characteristics of ventilation do not significantly affect performance.

The major advantages of a circle system used with a low flow are economy, reduction in atmospheric pollution and the conservation of heat and water vapour. At first sight the economic advantage would seem to be irrefutable—a 10-fold or more reduction in fresh gas flow. Nunn (1979) calculated that the use of a totally closed nitrous oxide–oxygen–halothane administration, as compared with a method using a 7-litre total fresh gas flow, resulted in a saving of about 75 cents (50p) per hour, a saving that is negligible in the context of the total cost of anaesthesia and surgery. Impressive sums can appear to be saved if aggregated over the course of a year for a large institute (Lowe and Ernst, 1983), but are still very small in comparison with the total cost of providing an anaesthetic service, and negligible in the context of the total cost of health care. Greater savings are made if more expensive agents are used, and a stronger (although still not overwhelming) argument can be made for the use of a low flow system if isoflurane is to be used. Against the savings made by using a low flow system must be offset the purchase and maintenance costs of any monitoring equipment needed to use low flow systems with safety.

By reducing the amount of gas delivered from an anaesthetic machine, low flow systems undoubtedly reduce the magnitude of the problems of pollution, but these techniques cannot totally solve the problem, as a complete anaesthetic administration cannot be totally closed. Regardless of the fresh gas flow or breathing system used, there are now available easily applied and effective methods of venting waste anaesthetic gases from the operating theatre. Heat and water retention in a circle system results partly from rebreathing of warm and wet expired gas and partly from heat and water liberation during carbon dioxide absorption. Gases do tend to cool as they traverse the circle system, but are still wetter and warmer than fresh gas delivered from an anaesthetic machine. On first principle this should be advantageous to the patient. In practice, it has been difficult to show any deleterious effects of dry gas inhalation for the (usually) limited duration of an anaesthetic administration (Knudsen, Lomholt and Wisborg, 1973).

The major disadvantage of a circle system used with a low fresh gas flow is that, as fresh gas flow is reduced towards a basal value, it becomes increasingly difficult to predict gas composition within the system and thus the composition of inspired gas. This results from the influences of gas uptake from the circle system gas by the subject. Such uptake has an increasing effect on circle gas composition as the magnitude of uptake approaches the magnitude of fresh gas flow. The magnitude of oxygen uptake by a subject can be predicted with moderate accuracy. It is more difficult to predict the magnitude of anaesthetic uptake. Major difficulties can arise in delivering adequate amounts of volatile anaesthetic vapour from conventional vaporizers placed in the fresh gas flow line. Some calibrated vaporizers may cease to function or function inaccurately at fresh gas flows of less than 0.5 litre min^{-1}. Lin (1980) showed that the Fluotec Mark III and similar vaporizers for halothane and enflurane behave with reasonable accuracy at flows down to 100 ml min^{-1}. The maximum output from a vaporizer limits the mass of anaesthetic that can be delivered to the breathing system. This is a problem which is greatest early in induction. It can be minimized by priming the circle system with a high concentration of anaesthetic vapour, or by using high flows at the start of the induction period. This problem of delivering an adequate mass of anaesthetic is less with Copper-kettle type vaporizers, which can produce metered amounts of saturated vapour of anaesthetic agents (Morris, 1979).

Use of a vaporizer within a circle system requires a simple vaporizer of low resistance. The danger of such vaporizers used with low flow techniques is that of excessive vaporization and the production of dangerously high vapour concentrations. This arises because vaporization is affected by ventilatory flow and independent of fresh gas flow. In-circuit vaporizers should not be used during controlled ventilation unless scrupulously accurate methods are available to monitor inspired gas composition. Use of such vaporizers during spontaneous breathing has an associated safety factor—excessive vaporization increases depth of anaesthesia and the associated respiratory depression leads to a diminution in the rate of vapour production. This safety factor relies on the production of what is invariably an excessive depth of anaesthesia, and must be considered a poor method of controlling anaesthetic administration.

Direct injection of liquid anaesthetic to the anaesthetic system is a technique which has been practised for many years (Jackson, 1915; Hampton and Flickinger, 1961; Wolfson, 1962). Liquid injection avoids the problems associated with vaporizers. Knowledge of the liquid density and molecular weight of an agent (and, ideally, the temperature inside the circle system) is needed to calculate the amount of vapour derived from a known volume of liquid. Liquid anaesthetic is best injected into the expiratory limb of a circle system. Great care must be taken that syringes containing volatile anaesthetics are not inadvertently used for i.v. administration.

Monitoring of circle gas composition

The considerable problems that arise in predicting inspired gas composition during use of low flow techniques can be greatly minimized by monitoring gas concentrations in tidal gas or in the circle system. Relatively cheap monitors of adequate accuracy are available to measure oxygen concentration and the concentration of volatile anaesthetic vapours. Use of an oxygen monitor should be considered mandatory when low flow techniques are used, especially if nitrous oxide is present in the circle system. Devices to measure volatile anaesthetic concentration, based on an infra-red or some other absorptive principle, are highly desirable, especially when liquid injection techniques are used. Monitoring of gas concentration does not obviate the need for close clinical observation.

Other considerations

Although it is possible to use a low flow technique from the start of anaesthetic administration, there are advantages in using high flow techniques in the early stages of induction. The problem of supplying adequate amounts of anaesthetic agents to satisfy uptake requirements is minimized and an initial period when a high fresh gas flow is used results in most of the nitrogen present in the subject's FRC being eliminated. Some nitrogen accumulation in a circle system used with low flows is unavoidable. Although there may be advantages in having nitrogen present in the system when fresh gas consists mainly of oxygen, it is usually advisable to minimize nitrogen concentration and the consequent dilutional effects. During established anaesthesia using low flow techniques, the considerable buffering actions of the circle system can produce difficulties if rapid changes in anaesthetic depth are required. Volatile anaesthetic concentration within the circle system can be reduced rapidly to near zero by using an absorber container filled with activated charcoal (Maggs and Smith, 1976; Ernst, 1982). The simplest way of establishing control over composition of gas in the circle system is to increase fresh gas flow to the system.

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VAPORIZATION AND VAPORIZERS

D. C. WHITE

THEORY

Kinetic theory

Matter is composed of small particles termed *molecules*, each of which exhibits the characteristic properties of the substance of which it is a constituent. These molecules are in constant, rapid motion.

In the *liquid state*, the motions of the molecules are less restricted than in the solid state, with each molecule having individual freedom of movement. Thus, a liquid has the property of mobility, whereby it can change its shape but maintain its volume (approximately), which indicates appreciable forces of cohesion between liquid molecules.

Vaporization of an exposed liquid occurs when the more energetic molecules have a sufficiently large upward velocity to carry them clear of the range of molecular attraction. The remaining molecules have a lower average kinetic energy and the temperature of the liquid mass decreases. Consequently, heat flows in from outside the system until any temperature gradient is removed. It is this heat which is the latent heat of vaporization (the heat required to convert a substance from the liquid state to the vapour without a change in temperature: usually measured in J mol^{-1}.

In the *gaseous or vapour state*, the distance between the molecules is at least 10 times as great as the average distance between molecules in the liquid state. Thus, the molecules escape almost completely from their mutual attractions. The random movement of vapour molecules sometimes brings them into range of the attractive forces associated with the mass of molecules in the liquid state, and the vapour molecules can be recaptured. Under steady temperature conditions a *dynamic equilibrium* is established between molecules in the liquid and vapour states (or phases) and under these conditions the pressure of the vapour is termed the *saturated vapour pressure* (sat.v.p.) at that particular temperature. Saturation can be achieved either by increasing the amount of the substance in the vapour state until the partial pressure is equal to the sat.v.p., or by reducing the temperature until the amount of vapour in the gas phase is enough to cause saturation at the new temperature (*the dew point*).

If the temperature of a vapour–liquid system is increased, the sat.v.p. increases. The relationship between sat.v.p. and temperature is given by the Antoine equation (Rodgers and Hill, 1978):

$$\operatorname{Log} P = A - \frac{B}{t+C}$$

where P is the pressure, t is the temperature (°C) and A, B and C are constants derived experimentally. Curves generated by Antoine equations for some common agents are shown in figure 1. There is a maximum temperature above which a liquid cannot exist—termed the *critical temperature*. Above this temperature, the substance can exist only in the gaseous phase.

Anaesthetic agents administered by inhalation must be capable of existing in gaseous form under ambient conditions of temperature and pressure. Such agents may be classified into two groups. The first group consists of anaesthetic gases such as nitrous oxide and cyclopropane, which at room temperature and pressure can exist only in gaseous form because that pressure is less than their vapour pressure at that temperature. Mixtures of known composition can be made of these agents with oxygen and other gases, and administered to patients by metering the gas flow from the cylinder in which the agent is packed. The second group, to which most anaesthetic agents belong, includes those which exist as liquids at normal room temperature and pressure. The gaseous phase of these liquids is conventionally termed a vapour.

The basic requirement for the administration of

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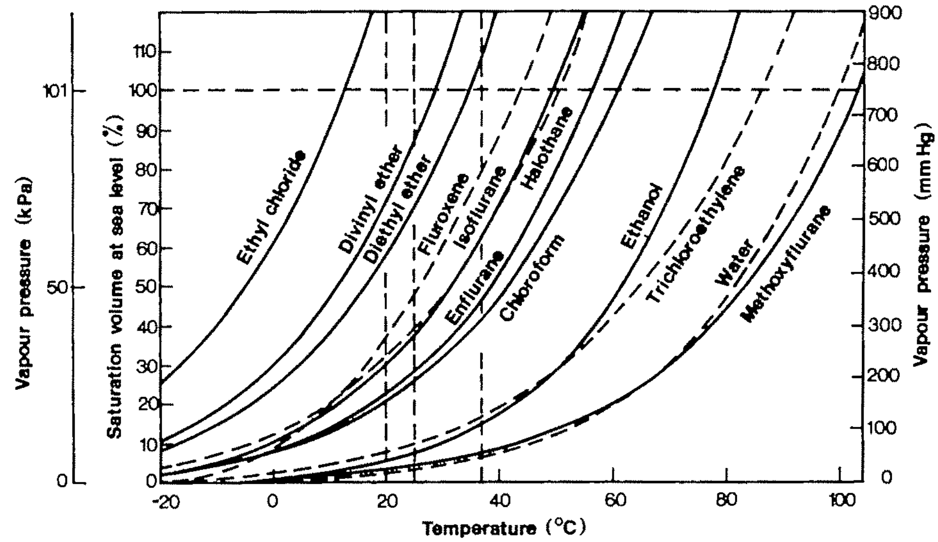

FIG. 1. Vapour pressure as a function of temperature for a number of agents. (Adapted with permission from Rodgers and Hill (1978).) The curves were generated by Antoine equations.

the anaesthetic vapours is the controllable production of the vapour from the liquid agent and the device in which this takes place is the vaporizer.

UNCALIBRATED VAPORIZERS

The simplest form of vaporizer is the napkin as used by Simpson with chlorofom in 1847. Ether or chloroform was dripped on to the cloth at an increasing rate and was there vaporized by the patient's breath passing through the cloth.

The napkin was soon replaced by various forms of wire framework which supported gauze or similar porous material away from the patient's skin. One problem with these simple devices is the decrease in temperature of the mask as a result of latent heat of evaporation. This decrease in temperature not only reduces the concentration of agent inspired, but it may also be sufficiently great to cause the water in the patient's expired air to freeze on the gauze, thus impeding the passage of air through the mask. A further problem with the "open drop" mask is the depression of inspired oxygen concentration caused by the presence of the anaesthetic vapour.

As soon as compressed gas became available in cylinders, it became possible to pass a gas stream over or through the liquid anaesthetic contained in a bottle. Most modern vaporizers belong to this category, to which the term "plenum" is applied. (A plenum is a chamber in which the pressure within is greater than the pressure without.) Plenum vaporizers are also referred to as flow-over vaporizers.

The most widely used uncalibrated plenum vaporizer has been the Boyle's Bottle, shown in cross section in figure 2. There are two controls, the lever which determines what proportion of the gas stream to the patient passes over the liquid where it picks up anaesthetic vapour, and the plunger which controls the cowl which regulates the proximity of the gas stream to the liquid. The controls of these simple vaporizers are not very precise, but the biggest cause of variable performance is the absence of any temperature compensation. As the vaporizer is used, the temperature decreases to an extent which has a very great effect on the output of the vaporizer. Figure 3 shows the effect of an 8-litre gas flow passed through a Boyle's bottle containing ether, when the gas is A passed over the surface, and B bubbled through the liquid agents. These two modes of operation produce markedly different temperature changes, but reference to figure 1 will show why the output concentration of the vaporizer is approximately the same after 10 min whichever mode is adopted. The rate of decrease of sat.v.p. with temperature is greatly reduced at low temperatures.

Discussion of uncalibrated vaporizers may appear to be of academic interest to the present day

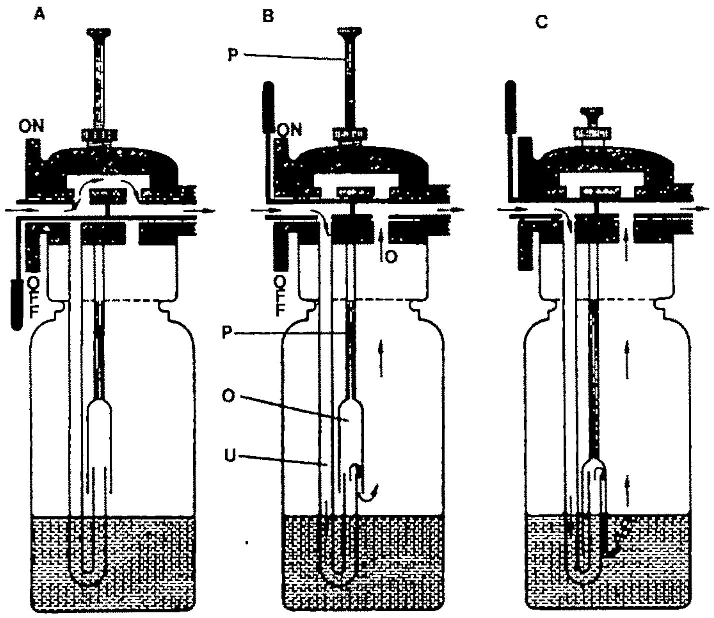

FIG. 2. Boyle's bottle (A) shows control lever in "off" position; (B) shows the plunger P partly depressed so that the gas passes over the surface of the liquid, and (C) shows the plunger fully depressed, lowering the cowl so far that gas bubbles through the liquid. U = U tube; D = outlet. (From Ward (1975) by courtesy of the author and Baillière Tindall.)

anaesthetist, but it can be argued that it is inherently safer to regulate the inspired concentration of anaesthetic by observing the patient's response without reference to the actual anaesthetic concentration than it is for the anaesthetist to impose on the patient a concentration of anaesthetic he believes to be correct.

CALIBRATED VAPORIZERS

Despite these considerations, modern vaporizers are calibrated: that is to say they are designed to produce accurately known concentrations of vapour in the clinical range. It is often stated that this became a necessity with the introduction of halothane in 1954 because, with this agent (and other modern agents), too high a concentration would be dangerous. Clinical experience suggests that the use of very high concentrations of any agent is potentially dangerous, but the older agents—in particular diethyl ether—were used in vaporizers with no temperature compensation and, as can be seen from figure 3, such vaporizers were not able to maintain high concentrations for very long and this contributed a built-in safety factor which was absent or reduced when the newer, less volatile agents were used in uncalibrated vaporizers with or without some attempt at temperature compensation.

Most vaporizers in current use are constructed on the principle shown in figure 4. The incoming gas flow is split into two channels, the main or bypass stream in which the flow per unit time is represented by V_{dil} and the vaporizing or carrier gas stream, V_{car}. In passing through the vaporizing chamber, V_{car} picks up a volume of anaesthetic vapour, V_{an}, and then rejoins V_{dil}, by which it is diluted to constitute V_{total}. The ratio in which the incoming gas stream is divided is known as the splitting ratio (Leigh, 1985) and this ratio is determined by the vaporizer controls, which are variable flow restrictors which are placed at the arrows 1 and either 2 or 3 in figure 4. In all modern vaporizers of this pattern, the constriction is at point 3, in order to minimize the pumping effect (see below). One of these variable restrictors constitutes the manual control of vaporizer output and the other the temperature-compensating control, which may be automatic.

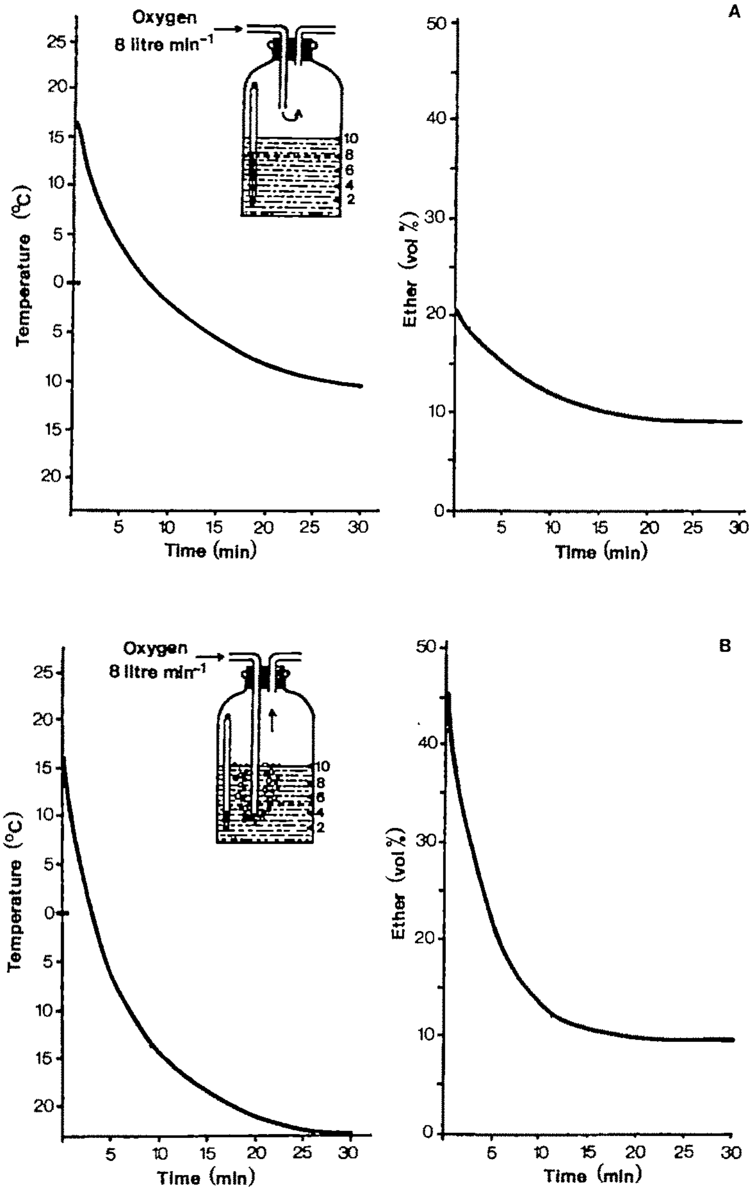

FIG. 3. Effect on temperature and vapour production of 8-litre gas flow through Boyle's bottle containing ether: (A) gas blowing over surface, and (B) bubbling through liquid. (From Macintosh, Mushin and Epstein (1963) by courtesy of the authors and Blackwell Scientific Publications.)

Calculation of vaporizer output

The anaesthetic vapour concentration in (vol %) is given by the expression:

$$\frac{V_{car} \times P_{an} \times 100}{V_{dil} \times (P_{bar} - P_{an}) + V_{car} \times P_{bar}}$$

where P_{an} is the partial pressure of anaesthetic vapour in the vaporizing chamber and is equal to the sat.v.p. at that temperature, and P_{bar} is the atmospheric pressure.

Problems in vaporizer design

Temperature control. As already described, the decrease in temperature on vaporization reduces vaporizer output, and the more volatile the agent,

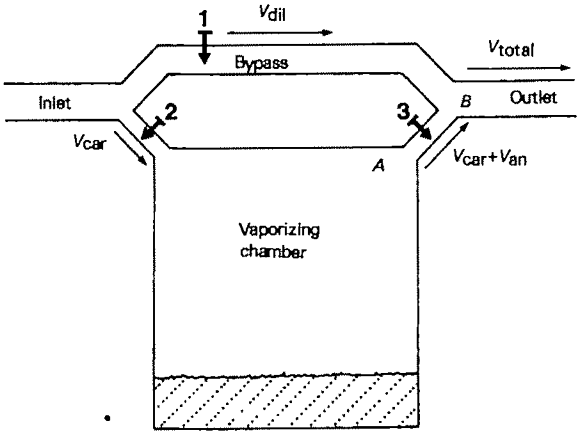

FIG. 4. Diagram of vaporizer to show position of controls and illustrate method of calculating anaesthetic concentration delivered. (Adapted from Rodgers and Hill (1978).)

the bigger is this problem. The simplest method of dealing with it is to display the temperature of the anaesthetic agent within the vaporizer by means of a suitably placed thermometer. Then, as the temperature decreases, the anaesthetist changes the splitting ratio so that a higher proportion of the total gas flow passes through the vaporizing chamber and the output from the vaporizer remains constant. This method is acceptable if the temperature change in clinical use is slow and small, and this may be achieved by constructing the vaporizer of large and heavy metal parts which act as a heat reservoir and prevent rapid temperature changes when the vaporizer is in use. Also required is a table showing how the sat.v.p. changes with temperature, to enable the splitting ratio to be correctly adjusted. More conveniently, this information can be displayed graphically on the dial of the control knob.

Alternatively, the process may be made automatic by arranging for the splitting ratio to be adjusted by a temperature-sensitive element such as a bimetallic strip or a bellows which changes volume with temperature. A third possibility is to maintain the vaporizing chamber at a fixed temperature by a thermostatically controlled heating element. Anaesthetists have been understandably wary of this last concept, since malfunction of the thermostat could severely affect the accuracy of the calibration and ultimately result in the agent boiling; however, vaporizers using this principle have now been constructed.

Level control. The change in level of liquid anaesthetic in the vaporizing chamber as it vaporizes may also affect the concentration delivered. Most vaporizing chambers contain some type of wicks which dip into the liquid agent and remain wet by capillary attraction, thus exposing a large wetted surface to the gas passing through the chamber. The depth to which the wicks are immersed affects the area of wick exposed to gas, and this could affect the efficiency of vaporization. One widely used type of vaporizer has been found to give a slightly higher concentration at a given setting when a quarter or half full than when filled to the "Full" mark (Ward, 1975).

The changing level of liquid anaesthetic is not a major problem in modern vaporizers and is dealt with by providing a generous area of wick and limiting the volume of liquid agent permitted in the vaporizing chamber.

Pumping effect (Hill and Lowe, 1962). In clinical use, the gas passing through vaporizers may be subjected to varying resistance to flow downstream of the vaporizer (frequently referred to as increased "back pressure"). The commonest cause of such variation is the use of ventilators of the minute volume divider type (such as the Manley) in which there is a build up of pressure before or during each inspiration. This increased pressure is transmitted back to the vaporizer and more gas flows into the vaporizing chamber through both the entrance and exit passages so that pressure in the vaporizing chamber will increase. When the resistance downstream decreases, the pressure in the vaporizer also decreases and a wave of vapour in excess of the normal, steady state flow passes into the output of the vaporizer, producing a wave of increased anaesthetic concentration. This is termed the "pumping effect" and, under optimum conditions, can intermittently double the concentration of vapour delivered.

The magnitude of the pumping effect depends on:

(a) the extent of the pressure fluctuations;
(b) the flow rates of gas through the vaporizer—the effect is greater at low flow rates; and
(c) the size of the vaporizing chamber—the smaller the chamber the less the effect (but the less room there is for vaporizing surfaces).

The pumping effect can be minimized in a number of ways:

(a) A pressurizing valve can be placed in the gas delivery pipe downstream of the vaporizer to smooth out the pressure fluctuations.
(b) The length of passageway between the splitting valve and the vaporizing chamber can be

increased so that it acts as a reservoir, absorbing the increased gas flow during a pressure wave and releasing it again without it having reached the liquid agent or, alternatively, preventing gas which has reached the agent entering the bypass stream. Coupled with this, the highest resistance in the vaporizing chamber pathway must be at the exit from that chamber (Hill, 1968).

(c) The vaporizing chamber must be of the minimum size compatible with efficient vaporization.

(d) Increasing the overall resistance to gas flow through the vaporizer reduces pumping and this trend can be clearly seen in vaporizer design.

(e) The vaporizer itself can be pressurized, thus preventing any pumping. An experimental vaporizer of this type is described below.

(f) Bubble-through vaporizers such as the Copper Kettle and the Halox (see below) can be rendered immune to pumping by fitting a one-way valve to the outlet from the vaporizing chamber.

(g) Injection of liquid anaesthetic into anaesthetic circuits (see below) is a method in which pumping can be prevented by ensuring that the injection is carried out at a pressure high enough to be unaffected by pressure changes in the anaesthetic circuit.

Flow sensitivity. It is desirable that a vaporizer output should be unchanged over a wide range of flow rates ranging from 250 ml min^{-1} (basal oxygen flow into a closed circuit) to as much as 12 litre min^{-1} (minute volume in a non-rebreathing system).

Older vaporizers were markedly deficient in this respect, but the most modern vaporizers do meet this requirement fairly well, except at the extremes of the flow rate range. This has been achieved by:

(a) Improving the efficiency of vaporizing chambers so that, even at high flow, gas leaving the vaporizing chamber is fully saturated.

(b) Operating the vaporizing chamber at a relatively high pressure (i.e. restricted outlet) in order to overcome the resistance to flow of the relatively dense saturated vapour, even at low flow rates (this also reduces pumping effect).

(c) Ensuring that the pressure/flow characteristics of the two gas passages within the vaporizer (the bypass and vaporizing channels) are as far as possible the same. This involves careful design of all controls and gas passages to maintain laminar flow and also results in modern vaporizers having a high overall resistance to gas flow. (The Mk I and II Fluotecs could be used as draw-over vaporizers.)

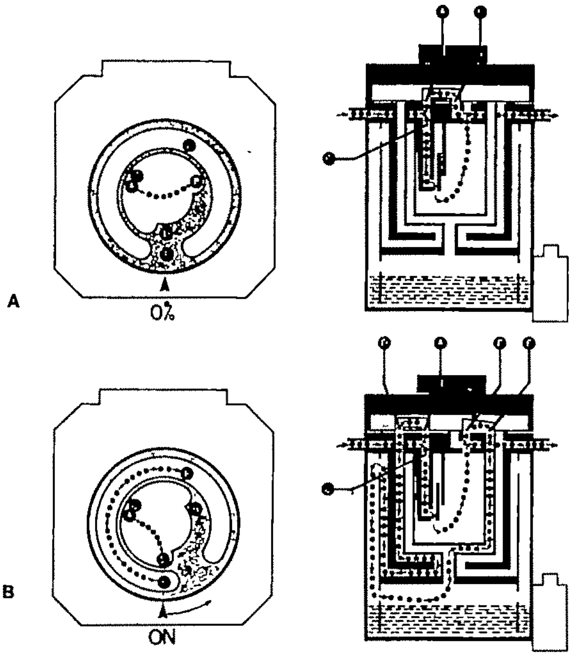

FIG. 5. Fluotec Mk 4 in (A) off position and (B) on position. Rotary valve (shaded): A = inlet; B = outlet; C = inlet to bypass channel (temperature control element); D = vaporizing chamber inlet; E = outlet from vaporizing chamber to calibration control; F = to vaporizer outlet. (Courtesy of Ohmeda Ltd.)

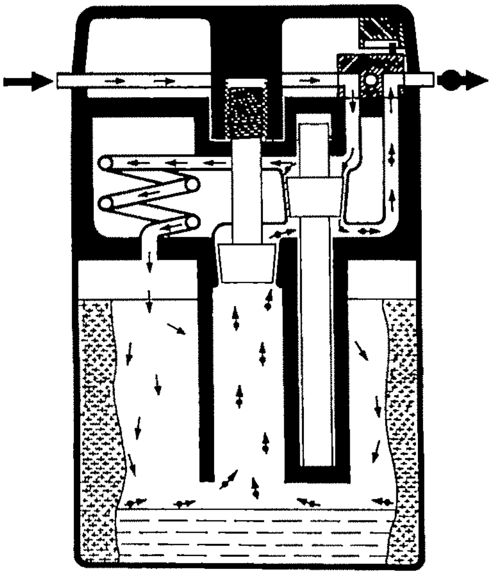

FIG. 6. Drager Vapor 19 Vaporizer. (Courtesy of Dräger Ltd.)

Modern Vaporizers

Two modern vaporizers are shown in figures 5 and 6.

Bubble through vaporizers

The Copper Kettle and the Halox vaporizers work on a principle which is basically the same as the vaporizers already described, but have considerable structural and operational differences. As shown in figure 7, the main gas flow (oxygen and nitrous oxide) is controlled by two rotameters and a small oxygen rotameter is provided to meter the gas (oxygen) passing through the vaporizing chamber. This consists of a copper vessel in the case of the Copper Kettle and a glass bottle in the Halox (fig. 8). Within the vaporizing chamber the gas is bubbled through the liquid anaesthetic via a sintered disc of bronze or glass, which breaks the gas stream up into very small bubbles, thus creating a large gas–liquid interface and ensuring that the gas leaving the vaporizing chamber to join the main gas stream is fully saturated with the agent. A thermometer is fitted into the vaporizing chamber so that, by reference to the graph of sat.v.p. against temperature, the concentration of agent leaving the vaporizing chamber is known and the concentration reaching the patient can be calculated simply.

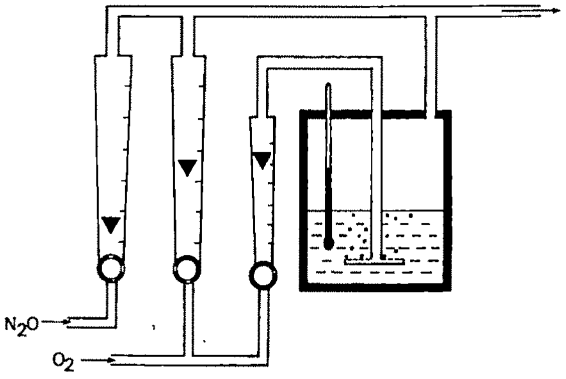

FIG. 7. Copper Kettle vaporizer.

Vaporizers working on this principle have a number of advantages, since rotameters and thermometers can be operated with considerable accuracy over a very wide range of total gas flow rates and anaesthetic concentrations, and, as noted above, they may be made immune to the pumping effect by a check valve. They are also highly versatile, since any agent can be used and the absence of wicks makes it possible to change the contents of the vaporizing chamber easily. A potential danger of these vaporizers is that any reduction in the main gas flow, such as a failure of the nitrous oxide supply, would result in a sharp increase in the anaesthetic concentration delivered. Finally, it has to be admitted that the necessity for calculation has impeded widespread use of these

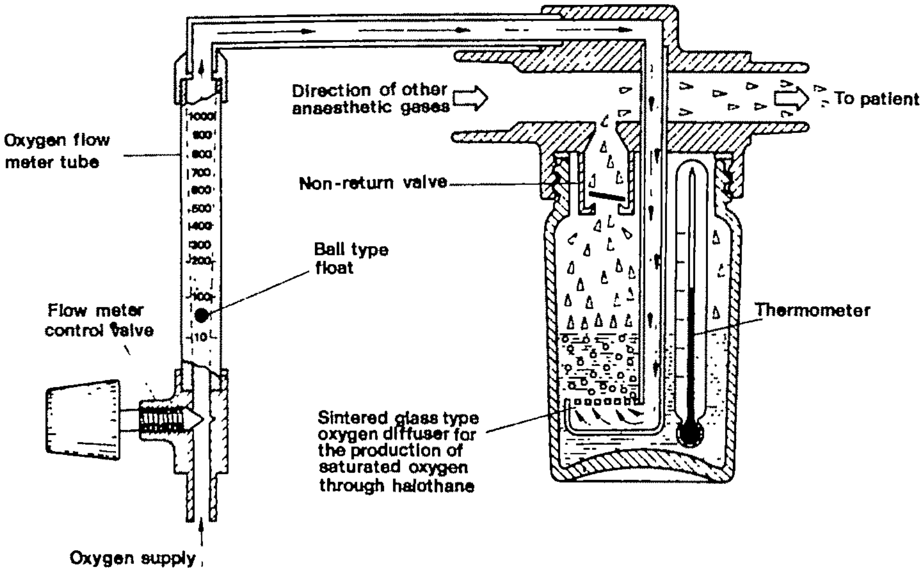

FIG. 8. Halox vaporizer. (From Ward (1975), by courtesy of the author and Baillière Tindall.)

vaporizers despite the fact it can be simplified readily to nomogram or slide rule form (Jennings, Taylor and Young, 1967).

Draw-over vaporizers

A draw-over anaesthetic system (fig. 9) is one in which the patient draws air in over the vaporizer by his own inspiratory efforts, expiration being to atmosphere via a non-rebreathing valve. This usage requires a specialized type of vaporizer, the principal feature of which must be the low resistance to gas flow so that the patient may breathe unimpeded. As might be expected, vaporizers of this type show very marked pumping effect if subjected to varying pressures so, if a draw-over system is to be used for intermittent positive pressure ventilation, it is important that the inflating bellows and associated valves are placed between the vaporizer and the patient so that the vaporizer is not subject to lung inflation pressures. An example of a draw-over vaporizer is given in figure 10.

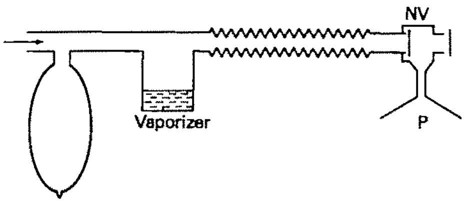

FIG. 9. Draw-over vaporizer and system.

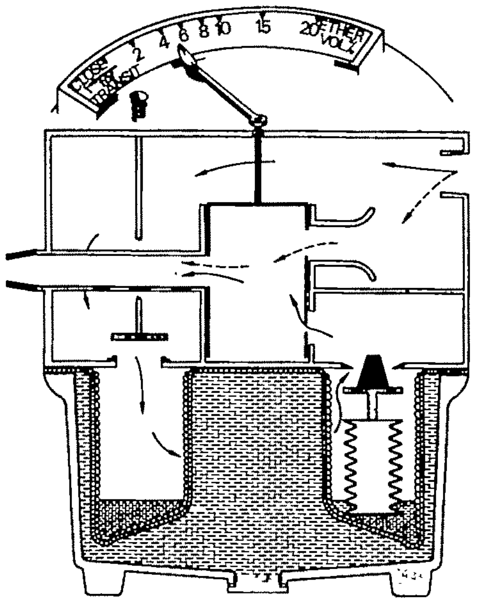

FIG. 10. EMO Vaporizer. (From Ward (1975), by courtesy of the author and Baillière Tindall.)

Closed-circuit vaporizers

The operation of vaporizers with closed-circuit anaesthesia systems was analysed by Mapleson (1960). He found that, if the vaporizer is placed outside the circle in the fresh gas flow (the VOC position), the concentration of anaesthetic in the circle cannot increase above that delivered by the vaporizer, provided patient uptake was normal. This is substantially correct but, if nitrous oxide is used, the rapid uptake in the first few minutes of anaesthesia may produce a temporary increase in the circle concentration above that delivered (second gas effect (Eger, 1974)).

If a completely closed-circuit technique is to be used from the beginning of the anaesthetic, the use of a vaporizer in the VOC position presents certain problems, particularly if it is intended to use nitrous oxide. The first problem is that the rate of uptake of volatile agent in the first few minutes of anaesthesia is so great that, with only the low basal fresh gas flow into the circle, a very high vapour concentration (close to sat.v.p.) of the agent is required. Only the Copper Kettle (bubble-through) type of vaporizer is capable of giving a sufficiently high concentration. If nitrous oxide is to be used, two further difficulties arise: even the Copper Kettle type of vaporizer will not give a sufficiently high anaesthetic concentration, since nitrous oxide dilutes the concentration of volatile agent; in addition, the uptake of nitrous oxide is changing so rapidly in the first 30 min of anaesthesia that continual adjustment of the vaporizer flow rates is necessary. If VOC is required, it is easier in practice to use a conventional vaporizer with a high gas flow and an open expiratory valve for a period at the beginning of anaesthesia and then reduce the gas flow to the basal value and close the expiratory valve.

Because of these complications with VOC, a vaporizer in the circle (VIC) is commonly used in closed-circuit anaesthesia, but there are difficulties here too. For use in this position (VIC), the vaporizer must have a low resistance to gas flow, since the patient is breathing through it. Also, the amount of anaesthetic which the vaporizer delivers into the circle is proportional to the gas flow through the vaporizer which, in this instance, is the patient's minute volume. The gas entering the vaporizer already contains anaesthetic and more is picked up on each circuit through the vaporizer, so that if mechanical ventilation is used (giving high minute volumes), dangerously high anaesthetic concentrations may build up. However, if the patient is breathing spontaneously, negative feedback occurs — if anaesthesia deepens then respiration is depressed and the inspired anaesthetic concentration decreases and anaesthesia lightens.

The requirement of low resistance to gas flow for vaporizers in the circle is the same as for draw-over vaporizers (discussed above), but not all vaporizers designed for the latter purpose are suitable for use in the closed circle. This is because the gas passing round the circle is fully saturated with water vapour and this tends to condense out in the vaporizer, particularly on any wicks, because of the low temperature at this site and the water or ice deposited may seriously affect the performance of the vaporizer (Ward, 1975).

The Goldman vaporizer has been used frequently in the VIC position in closed and low-flow systems (Goldman, 1962; Jordan and Bushman, 1981). This is a simple vaporizer having a small glass bowl and a tap with three positions diverting gas flow over the surface of the halothane within the bowl. Laboratory evaluation (Bushman et al., 1977) suggested that reducing the volume of intermittent gas flow through this vaporizer (i.e. simulated respiratory depression) resulted in alarming increases in the halothane concentration delivered, but clinical experience with the vaporizer in a closed circuit clearly showed the negative feedback effect described above (Barton and Nunn, 1975). This limits the inspired anaesthetic concentration during spontaneous breathing.

The problems of vaporizers and closed circuits are largely overcome by injecting liquid anaesthetic to the system.

Injection of liquid anaesthetic to breathing systems. One of the very first anaesthetic vaporizers (Gould and Morton, 1847) used a drip feed of ether onto a sponge located in the breathing system, and since then the principle has been widely used in anaesthetic equipment. If the volume of gas to which an injection of known amount of anaesthetic is being made is known, accurate control of vapour concentration is possible, as demonstrated by Clover's chloroform apparatus (Traer, 1862). This was not the case

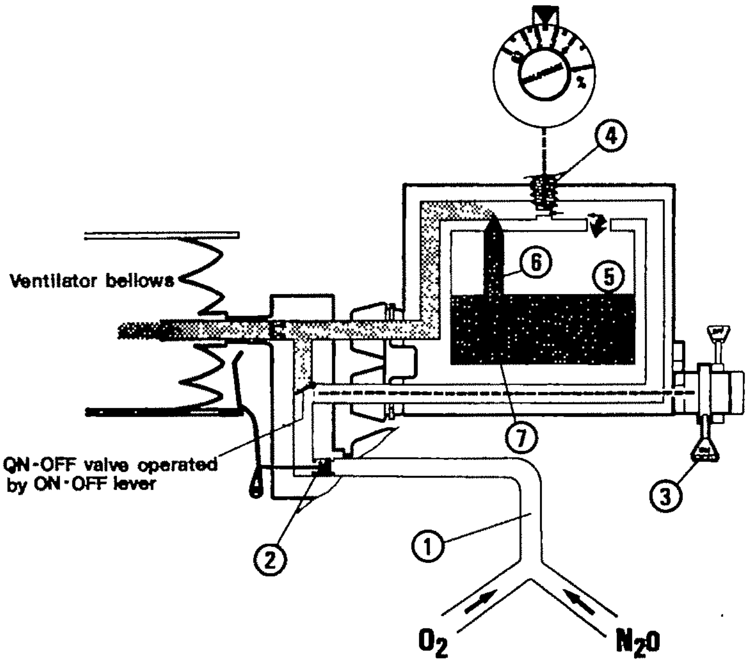

FIG. 11. Siemens vaporizer. 1 = Gas supply; 2 = control from ventilator; 3 = on–off control; 4 = vapour concentration control producing positive pressure in reservoir 5; 6 = injector nozzle; 7 = check valve retaining column in injector. (Courtesy of Siemens-Elema.)

with the numerous "drip feed" devices which have been used in the past, in which the rate of the gravity controlled drip was affected by pressure changes in the breathing system and no measurement of the volume of agent was made.

A modern vaporizer using direct injection is the Siemens–Elema (fig. 11). In this device, which is similar to a carburettor, the liquid anaesthetic is contained in a pressurized reservoir and injected, via a fine orifice, to the gas stream filling the bellows of a ventilator. The pressure in the reservoir is controlled by the gas flow rate past the vaporizing orifice, so that the proportion of liquid and gas are kept constant. This vaporizer demonstrates some of the virtues of liquid injection—thermal compensation is unnecessary, a wide range of rapidly changing gas flow rates can be accommodated without loss of accuracy, and a simple functional check of calibration accuracy can be made by measuring the rate of decrease of liquid agent with known gas flow rates—in this case, ventilator settings.

The viscosity of the vaporizing gas mixture does affect the calibration of vaporizers working on this principle and the effects of different mixtures of air, oxygen and nitrous oxide on the Siemens–Elema vaporizer are shown in figure 12. The effects of different gas mixtures on more conventional vaporizers are described below.

The injection of liquid anaesthetics has considerable advantages in the completely closed circuit, since it overcomes the problems with vaporizers described above. A vaporizer has been developed for this purpose in which the fresh gas flow into the circle is used to nebulize the liquid agent pumped to an adjacent jet (Salamonsen, 1978). Liquid anaesthetic injected directly to the circle is vaporized adequately by the minute volume passing round the system and programmed anaesthesia can be conducted using liquid anaesthetic, by injecting increments or by continuous infusion with an electrically driven syringe pump. The rate of injection is controlled by prediction of the patient's anaesthetic uptake based on anthropometric measurements (Lowe and Ernst, 1981) or, alternatively, may be controlled by continuous measurement of the arterial blood anaesthetic concentration derived from the end-tidal anaesthetic concentration (Ross et al., 1983).

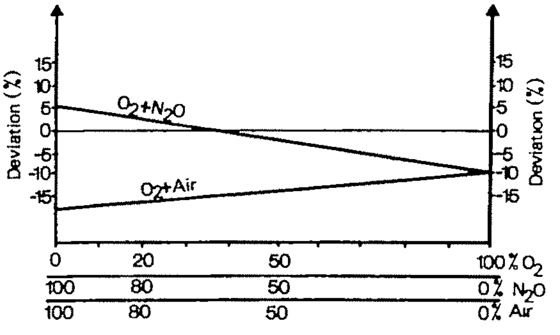

FIG. 12. Deviation from calibration of Siemens ventilator as a result of gas mixtures of differing viscosities. (Courtesy of Siemens Elema.)

The vaporization of agents in this way, directly in the circle, has certain dangers. One is that liquid anaesthetic may enter the patient's airway. This is guarded against by ensuring that the injection port is below the level of the airway, so that any liquid cannot run in, and by ensuring that the glass syringe containing anaesthetic is below the injection port, so that liquid cannot syphon into the circle.

Halothane contains 0.01% thymol as a stabilizer which, in a conventional vaporizer, remains in the liquid in the vaporizing chamber (see below), but may possibly be inhaled by the patient if the direct injection technique is used. The volatility of thymol is so very low (boiling point 233 °C) that this seems unlikely, and no problem has been reported, despite considerable use of this technique.

Pressurized vaporizers

A variant of vaporizer design is the pressurized device described by Titel and colleagues (1968), in which the vaporizing chamber is pressurized to pipeline pressure (5 atmospheres absolute or 5 ATA). The sat.v.p. of the agent in the vaporizing chamber remains unchanged—in the case of halothane it is approximately 0.3 ATA, so that the saturated gas leaving the pressurized vaporizing chamber contains only 6–7% v/v of halothane. The high pressure stream of gas and vapour then joins the bypass gas stream and is diluted as in a conventional vaporizer. In this vaporizer, temperature compensation is effected by varying the pressure in the vaporizing chamber. As might be expected, this vaporizer is not subject to the pumping effect.

Ultrasonic vaporizers

An anaesthetic vaporizer using an ultrasonic nebulizer has been constructed and used experimentally (Cabler, Geddes and Rosborough, 1975).

Nebulizers disperse liquids into small droplets and clearly this facilitates vaporization, but it would be important to ensure that there was no risk of the inhalation of droplets of liquid agent.

Performance

Units of calibration

The output of anaesthetic vaporizers is usually expressed in volumes %, that is volume of anaesthetic vapour/volume of gas × 100, and under most circumstances this is satisfactory. However, vol % is a ratio only, and if a vaporizer is used under conditions of abnormal pressure such as at high altitudes or in a hyperbaric chamber, these units can be misleading (see below). Under these circumstances the anaesthetic concentration is best expressed as an absolute value such as mg $litre^{-1}$ of anaesthetic vapour per litre of gas or, more usefully, as a partial pressure.

Effect of ambient pressure on vaporizer performance

If a vaporizer of the Fluotec type is used in a hyperbaric chamber at 2 ATA, the partial pressure of halothane coming from the vaporizing chamber remains unchanged at approximately 0.3 ATA, but at an overall pressure of 2 ATA this is only 15% instead of 30% at 1 ATA. The concentration of halothane in the output of the vaporizer is therefore halved if expressed as vol %, but remains unchanged if expressed as a partial pressure. Anaesthetizing potency is determined by partial pressure. Operation under reduced ambient pressure, such as at high altitude, produces effects in the opposite direction.

Other minor deviations in vaporizer performance might be expected at abnormal pressures resulting from changes in gas viscosity affecting the pressure/flow characteristics of the gas channels and altering the splitting ratio. For a fuller discussion of the effect of ambient pressure changes on different types of vaporizer, the reader is referred to Schreiber (1972).

Effect of carrier gas composition on vaporizer performance

It was observed during the evaluation of the MK3 Fluotec vaporizer (Paterson, Hulands and Nunn, 1969), that differences in carrier gas composition (100% oxygen or 35% oxygen + 65% nitrous oxide) could affect the performance of vaporizers and since then a number of studies and observations on this subject have been published (Diaz, 1976; Prins et al., 1980), the most recent and detailed being that of Palayiwa, Sanderson and Hahn (1983). The following is an attempt to summarize this complex subject.

Anaesthetic vaporizers are usually calibrated using oxygen as the carrier gas. The flow characteristics of oxygen and air are similar, and little change in calibration is seen if air or air and oxygen mixtures are substituted. If nitrous oxide in the concentrations used clinically (e.g. 66%) is added to the oxygen, two effects are seen on anaesthetic concentration, one temporary and one permanent. The temporary effect is a reduction in anaesthetic concentration and it can be, at least in part, ascribed to the nitrous oxide dissolving in the liquid agent in the vaporizing chamber (Gould, Lampert and Mackrell, 1982) so that, until the liquid is saturated, less gas is leaving the vaporizing chamber than might be expected. The duration of this effect depends on the gas flow rate and the volume of liquid anaesthetic involved. The permanent effect is more complex and results from the different physical properties of oxygen and nitrous oxide. The kinematic viscosity (viscosity/density) of nitrous oxide is one-half that of oxygen and this determines the critical flow rate above which turbulent flow appears, with a resulting increase in resistance. The addition of nitrous oxide may result in turbulent flow at narrow orifices and valves in the vaporizer where 100% oxygen was passing smoothly in laminar flow. The effect of this on the vaporizer, whether it increases or decreases, depends entirely on the detailed construction of the vaporizer and the precise location of the various narrow orifices.

The available data suggest that the magnitude of these changes is not sufficiently great to be of clinical importance, except possibly at very low gas flow rates such as in closed circuit anaesthesia (Lin, 1980), or if unusual gases such as helium form part of the carrier gas mixture.

Contamination of in series vaporizers

If two or more vaporizers of conventional pattern and charged with different agents are mounted in series and used simultaneously, some of the vapour from the upstream vaporizer dissolves in the liquid in the downstream vaporizer. This has the effect of diminishing the concentration of upstream agent coming out of the downstream vaporizer, and of contaminating the liquid in the downstream vaporizer so that, if it is used subsequently on its own, a mixture of the two agents emerges from the downstream vaporizer. It is recommended (Dorsch and Dorsch, 1973; Murray, Ssigmond and Fleming, 1973) that this effect can be minimized if the agent with the higher boiling point (lower sat.v.p.) is always placed upstream. The reason for this is that the contamination takes place in the downstream vaporizing chamber and, therefore, the proportion of total gas flow passing through this chamber must be minimized. This is accomplished if the lower boiling point agent is downstream because, in this vaporizer, a lower proportion of the total gas flow is passed through the vaporizing chamber than in the upstream (higher boiling point) vaporizer for a given dial setting.

It has been recommended that vaporizers should be mounted in parallel to avoid risks of cross-contamination. This would involve another control tap and would, of course, prevent the simultaneous use of two agents, unless further complex plumbing arrangements were made.

Incorrect filling of agent-specific vaporizers

As already described, vaporizers of the Copper Kettle type may be used with any volatile agent provided its physical characteristics are known, but vaporizers of the Fluotec type are designed for use with one agent only and filling devices are provided to prevent filling with the wrong agent. However, if this does occur, the output concentration of the wrong agent may be calculated using the formula given previously (under calculation of vaporizer output). This assumes that the vaporizer was empty before it was filled with the wrong agent. A more likely accident is the refilling of a partially empty vaporizer with the wrong agent, resulting in a mixture of approximately 25% of correct agent and 75% of wrong agent.

The vaporization of mixed anaesthetic agents was investigated by Bruce and Linde (1984), who studied mixtures of halothane and isoflurane and of halothane and enflurane. Theoretically, if the agents formed ideal solutions, then the vapour pressure attributable to each agent above the mixtures would be proportional to the molar proportions of the mixture. This may well be the case for mixtures of isoflurane and enflurane, because of the close similarity of their molecules, but for the mixtures investigated it was found that there was a departure from the ideal such that halothane facilitated the vaporization of both isoflurane and enflurane and in the process its own vaporization was also facilitated. If, therefore, a partially empty vaporizer is filled with the wrong agent, the composition of the vaporizer output cannot be calculated from a knowledge of the composition of the mixture (with the possible exception of enflurane and isoflurane mixtures), but the concentrations of the vapours of the two components are greater than predicted by assumptions of ideality.

Thymol

This substance, in a concentration of 0.01% w/w, is added to halothane as an antoxidant but, since it has a boiling point of 233 °C, it cannot be regarded as volatile and tends to accumulate in halothane vaporizers, where it is considered to clog up taps and have other undesirable effects (Balil, 1977; Milligan and Rodgers, 1983). Because of this, the regular drainage of halothane vaporizers is recommended, but often not carried out. In a survey of 28 halothane vaporizers in a Helsinki operating theatre suite, Rosenberg and Alila (1984) found that thymol had accumulated to up to 19 times the normal concentration, but there was no correlation between the thymol concentration and the inaccuracies found in the calibration of the vaporizers.

The absence of any stabilizing additive in enflurane and isoflurane is considered one of the advantages of these agents, but contamination producing yellow coloration has already been reported for isoflurane (Gandolfi, Blitt and Weldon, 1983) and for enflurane (Wald, 1981). This is attributed to substances leached out of plastic components of the vaporizer or, alternatively, to sulphur from the wicks.

Accuracy of vaporizer calibration

Modern vaporizers are robust and accurate devices, but their design embodies a variety of compromises and the manufacturers' specification usually indicates the resulting departures from perfection. Checking the accuracy of vaporizers is not easy, and even the most expensive laboratory anaesthetic gas measuring equipment itself requires very frequent calibration with volumetrically prepared standard gas samples of high standards if accurate measurements are to be maintained. If this is not undertaken, the measurements are themselves more likely to be inaccurate than the vaporizer.

Some anaesthetists attach great importance to the accuracy of vaporizer calibration, which is surprising when it is remembered what good results could be obtained from completely uncalibrated vaporizers. One authority has declared that most vaporizers today perform in the range of ±20% (Schreiber, 1972) and this appears entirely adequate for clinical purposes. Whatever the accuracy of the vaporizer, close observation of the patient and adjustment of anaesthetic concentration in the light of these observations is of much greater importance than accurate knowledge of the concentration delivered by the vaporizer.

Future Developments

The chief problems encountered with the present flow-splitting plenum type vaporizers using surface vaporization are those of exactly equalizing the pressure/flow characteristics of the two channels through the vaporizer under all conditions of operation, and of protecting the vaporizing chamber against the pumping effect.

Vaporizers of the Copper Kettle type have certain advantages; they can be made to work accurately over a very wide range of gas flow (Gartner and Stoelting, 1974) because the two channels (vaporizing and main flow) are controlled independently and not interactive. Pumping effect can be minimized by using pressure compensated rotameters and a valve protecting the vaporizing chamber. Fluidic control devices can be used with vaporizers working on this principle giving pulsed flows through both channels and changing anaesthetic concentration by varying the mark/space ratio. Vaporizers utilizing these principles are in experimental use and will be seen in the future.

The greatest number of advantages appears to lie with the principle of liquid injection. As can be seen from the Siemens vaporizer described above, this overcomes a number of the problems of current vaporizers, such as accuracy over wide ranges of gas flow, temperature control and pumping effect. Perhaps the most important virtue of liquid injection is that it lends itself to electronic control.

Another development of importance is the increasing availability of anaesthetic gas analysers for easy use in the operating theatre, using either well established techniques such as infra-red spectophotometry (Luff and White, 1985) or newer sensors such as the coated crystals of the Engström Emma. The widespread use of such analysers in anaesthetic equipment would greatly simplify vaporizer design, since accurate vaporizer calibration would become quite unnecessary and all that would be required of the vaporizer would be reasonable stability of output and a wide range of approximately linear control.

Finally, the availability of fast responding anaesthetic gas analysers capable of recording end-tidal anaesthetic concentration linked to a liquid injection vaporizer would provide servo control of arterial anaesthetic concentration and requires only a signal indicating the depth of anaesthesia to constitute an automatic anaesthetic machine.

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PAEDIATRIC ANAESTHETIC EQUIPMENT

D. J. HATCH

Paediatric anaesthetists and those working in designated paediatric centres are accustomed to having a wide range of apparatus available and equipment that is in regular use being in good working order. Tracheal tubes have normally been precut to the correct length and complete sets of tracheal tube connectors of all types are readily at hand. Anaesthetists who work in an environment where infants and children appear only occasionally are often less fortunate. The range of available equipment is usually far less wide, items which have not been used for some time may have fallen into disrepair, and vital sizes of tubes or connectors may be missing. The giving of even a relatively straightforward anaesthetic may become a nightmare in these circumstances, and accepting less than ideal items of equipment may well cause hazards to patient safety. Accepting a tracheal tube which is 0.5 mm too small in a neonate, for example, may cause unacceptably high airway resistance, and one that is too large may lead to severe stridor on extubation and possible subglottic damage. Deficiencies in equipment have been blamed for deaths in young children (Edwards et al., 1956). It is essential, therefore, that all anaesthetic departments should have a reliable system for ensuring that equipment comes up to the high standard required for paediatric anaesthesia. It may be wise for one member of the consultant staff to be given special responsibility for paediatric equipment, and inventories should be established against which all items can be regularly checked.

BREATHING SYSTEMS

The most important factors in the design of breathing systems for infants and young children are minimal resistance to airflow, low deadspace, lightness, reliability and ease of use. The ability to conserve heat and reduce water vapour losses, although important in intensive care and during long operations, is not generally thought to be a major consideration in operations of average duration. In centres where cyclopropane is still used, conductivity is essential.

Resistance

During laminar flow through tubes the Hagen–Poiseuille equation applies:

$$Q = \frac{\pi p r^4}{8ln}$$

where Q is flow, p the pressure change across the tube, r the radius, l the length and n the viscosity of the gas. Thus, pressure across the tube, and hence resistance, at a given flow rate increases according to the fourth power of any reduction in radius, causing a marked increase in the work of breathing during spontaneous ventilation. From the point of view of resistance, therefore, paediatric breathing systems should contain relatively wide-bore tubing, although increase in size may increase deadspace and make the system unnecessarily bulky. In practice, tubing with an internal diameter in excess of 1 cm is acceptable for children of weight up to 20–25 kg.

Unidirectional valves add extra resistance to the system. When a disc valve is closed, pressure is required to lift it from its seat before gas can flow. This pressure is defined by the equation:

$$P = \frac{4W}{\pi D^2}$$

where W is the weight and D the diameter of the disc (Hunt, 1955). Thus pressure required to open the valve is least with lightweight discs of large diameter. The opening pressure is increased by approximately 0.25 cm H_2O regardless of flow, when the disc is wet, because of the need to overcome the surface tension of the water. Once the valve is open, resistance to flow is determined by its size and shape. Nunn and Ezi-Ashi (1961)

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showed that the addition of resistances as low as 2 cm H_2O litre^{-1} s^{-1} to breathing systems in adults had a significant effect on respiration. A typical paediatric disc valve has a resistance of 3.5 cm H_2O litre^{-1} s^{-1} at 5 litre min^{-1} (Gregory, 1983). Valves also have a tendency to stick from time to time, and although they are used satisfactorily in paediatric circle systems such as the Bloomquist (Bloomquist, 1957) and Ohio (Dorsch and Dorsch, 1975), they have not gained wide popularity. Both Stephen and Slater (1950) and Adriani and Griggs (1953) noticed undesirable effects on respiration in infants. The use of circulators (Roffey, Revell and Morris, 1961) overcomes this problem, but these require special equipment and are not commonly used in paediatrics.

Valveless systems such as the "to-and-fro" absorption system have been made in a miniaturized form with small soda-lime canisters. These canisters do, however, increase resistance, and deadspace increases progressively as the soda-lime is exhausted. They are also slightly cumbersome to use and carry the additional risk of alkaline dust being inhaled by the patient. The most commonly used breathing system for children weighing less than 20–25 kg is some version of the Mapleson E or D system (Mapleson, 1954). The original T-piece (Ayre, 1937) was modified by Rees (Rees, 1950, 1960), who added an expiratory limb to prevent air dilution and an open-ended 500-ml reservoir bag to allow respiration to be monitored and positive pressure ventilation to be applied (fig. 1). Resistance is not a significant problem with tubing of 1 cm diameter, unless the length of the expired limb is excessive.

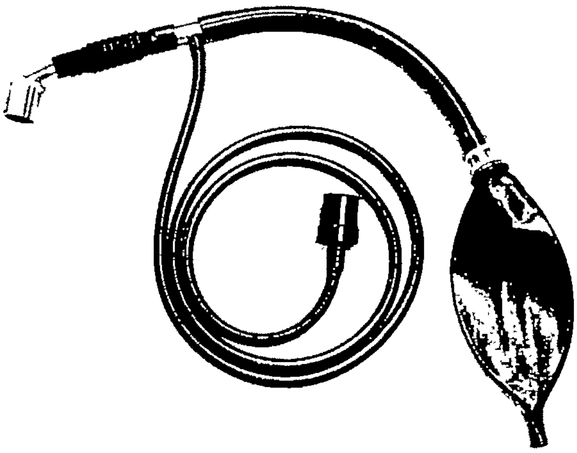

FIG. 1. The Rees modification of Ayre's T-piece with Levin's face mask adaptor and open-ended reservoir bag. (From Hatch and Sumner (1981).)

Deadspace

Values for deadspace (V_D), tidal volume (V_T) and V_D/V_T ratio when related to body weight in children are similar to those in adults (Brown and Fisk, 1979), so that a 3-kg infant with a tidal volume of 21 ml (7 ml kg^{-1}) and a V_D/V_T ratio of 0.3 has a deadspace volume of 7 ml. V_D/V_T increases as V_T decreases during deep anaesthesia with spontaneous ventilation. Deadspace can be increased significantly by the apparatus deadspace of masks and breathing systems unless steps are taken to minimize it. The Rendell-Baker mask and airway divider help to solve this problem, as does tracheal intubation. The deadspace of "to-and-fro" systems increases as the soda-lime becomes exhausted, and unacceptably high deadspace may also exist in circle systems, although this is reduced by the use of a circulator.

The effective apparatus deadspace of the T-piece or Bain systems, the characteristics of which are indistinguishable (Rose, Byrick and Froese, 1978), depends on the fresh gas flow rate (FGF) in addition to the apparatus volume between the patient and fresh gas inlet. The behaviour of these systems during spontaneous and controlled ventilation has been studied extensively and several formulae have been suggested for calculating the FGF required to avoid rebreathing. During spontaneous ventilation, inspired carbon dioxide increases when FGF is less than 2.5–3 times the minute volume (Lindahl, Charlton and Hatch, 1985). Because of the difficulty of measuring minute volume, Froese and Rose (1982) suggested that a flow rate of $3 \times (1000 + 100 \text{ ml kg}^{-1})$ would avoid rebreathing in children weighing between 10 and 30 kg. Lindahl, Hulse and Hatch (1984) suggested a flow of 15 × respiratory frequency × weight as an alternative. It is clear that a small amount of rebreathing may occur without any ventilatory response, since inspired carbon dioxide may not reach the alveoli.

The effect of rebreathing with a given FGF depends upon the respiratory waveform. Theoretically, when FGF is reduced, rebreathing com-

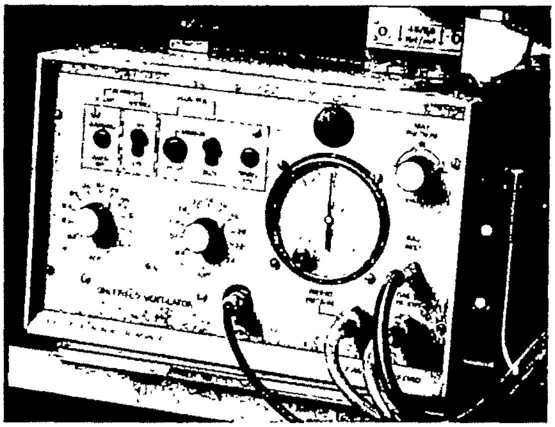

FIG. 2. The Sheffield Infant T-piece occluding ventilator.

mences late in inspiration (Sykes, 1968) and, if the volume of alveolar gas rebreathed is small, it does not pass beyond the anatomical deadspace. Meakin and Coates (1983) suggest FGF need not exceed minute volume, although Charlton, Lindahl and Hatch (unpublished observations) feel that, in order to allow an adequate margin of safety, FGF of 1.5–2 times minute volume should be used. For children exceeding 20–25 kg in weight breathing spontaneously, many anaesthetists prefer the Mapleson A breathing system (Magill attachment), where FGF as low as 50–70% of minute volume has been advocated (Kain and Nunn, 1968; Norman, Adams and Sykes, 1968).

During controlled ventilation, the T-piece may be used either with manual compression of the reservoir bag whilst the open limb is simultaneously occluded, or in conjunction with a ventilator. T-piece occluders, such as the Sheffield (fig. 2) or Amsterdam ventilators, rely on FGF to inflate the lungs, and require relatively high flow rates (2–3 times the minute volume). When ventilators with a separate source of driving gas, such as the Penlon Nuffield 200 (fig. 3), are used, FGF can be adjusted separately to avoid hypocapnia. Although more rebreathing does occur with the relatively high peak flows seen during controlled ventilation, normocapnia can be maintained with FGF as low as 1000 + 100 ml kg^{-1} if minute volume is at least 1.5 times FGF (Rose and Froese, 1979). Most authors recommend a minimum FGF of 3 litre min^{-1}. During controlled ventilation the Bain system behaves in a manner identical to the T-piece.

Lightness and ease of use

It is not yet clear if the recently introduced ADE breathing system (Humphrey, 1983) will gain popularity for paediatric anaesthesia, despite its obvious attractions. At present, the T-piece remains the least cumbersome breathing system for infants and young children, with the Magill attachment or Bain system being popular for older patients. The latter is difficult to sterilize.

The T-piece is not easy to scavenge, and the fitting of scavenging devices to the bag-tail seriously detracts from the basic simplicity of the

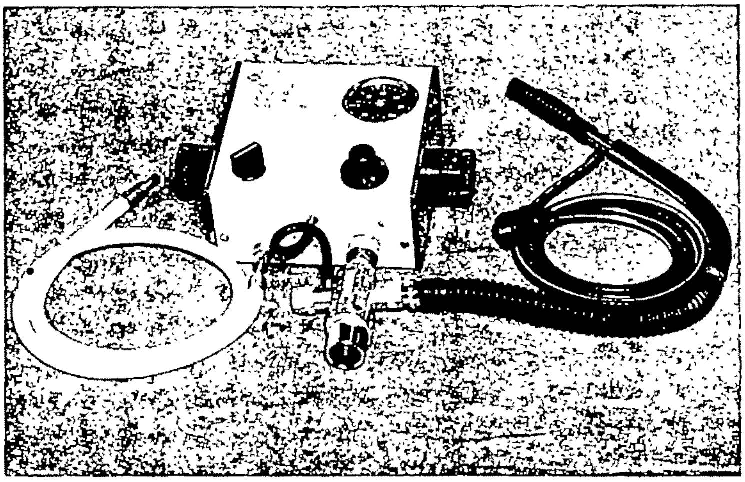

FIG. 3. The Penlon Nuffield 200 infant ventilator with Newton valve which allows tidal volumes as low as 10–20 ml to be delivered.

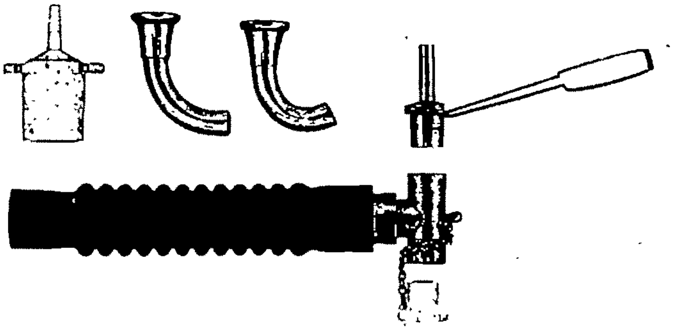

FIG. 4. High and low resistance tracheal tube connectors (from left to right): 15-mm taper (high resistance); Magill nasal, Magill oral, Tunstall/Oxford (8.5 mm) (all low resistance).

system, increasing the risk of exposing the airway to high pressures and of kinking or disconnection of the system. Exhaust gases can be removed safely by use of a scavenging dish with no direct contact with the T-piece (Hatch, Miles and Wagstaff, 1980).

BREATHING SYSTEM CONNECTORS

One of the most frustrating experiences in anaesthesia is to be faced with incompatible breathing system connectors, and attempts at standardization are to be encouraged. The subject is not, however, as straightforward for paediatric systems as for adults, since the 15-mm male tracheal tube connector is often too bulky for use in neonates and infants (fig. 4). The sudden change in diameter from a 2.5-mm tracheal tube to a 15-mm connector also causes turbulent flow with increased resistance (Hatch, 1978). There is wide support for a smaller standard to be adopted for paediatric tracheal tube connectors, such as the 8.5-mm used in the Oxford, Tunstall or Inkster connectors (Inkster, 1981). Manufacturers should be encouraged to develop disposable 8.5-mm connectors as an alternative to the 15-mm connector for use with the smaller sizes of tracheal tubes. Fortunately, the International Standards Organization has accepted the common practice of using an elastomeric tracheal tube adaptor (catheter mount) which can be fitted to low resistance tracheal tube connectors such as the Magill or Cardiff. Despite its shape, the latter has a surprisingly low resistance, and allows very secure fixation for oral tubes, together with a removable cap for tracheal aspiration. Other paediatric connectors include the Worcester and Ozorio used during pharyngeal surgery, and the Knight male and female connectors. Adult connectors can be used in older children. In the original T-piece illustrated in figure 1, the catheter mount and expiratory limb tubing are both pushed directly over the metal T-piece, but a version incorporating 15-mm tapered connections is available. This, however, is more liable to disconnection, and even misconnection, than the original.

TRACHEAL TUBES

The shape of the larynx in children is quite different from the adult, with a gradual reduction in diameter down to the subglottic or cricoid area, which is the narrowest part of the upper airway. Because the cricoid is a complete ring of cartilage, there is no room for expansion at this point, and any oedema will reduce the internal diameter. For this reason, and because this gradually tapering laryngeal shape provides a large enough area of contact with a tracheal tube to prevent aspiration, cuffed tubes are not used in children younger than 8–10 yr. Cuffs also effectively reduce the lumen and increase the resistance of the tube.

A wide range of tracheal tubes, both disposable and reusable, have been used over the years (fig. 5). More recently, disposable pre-formed tubes have become increasingly popular (fig. 6). Rubber

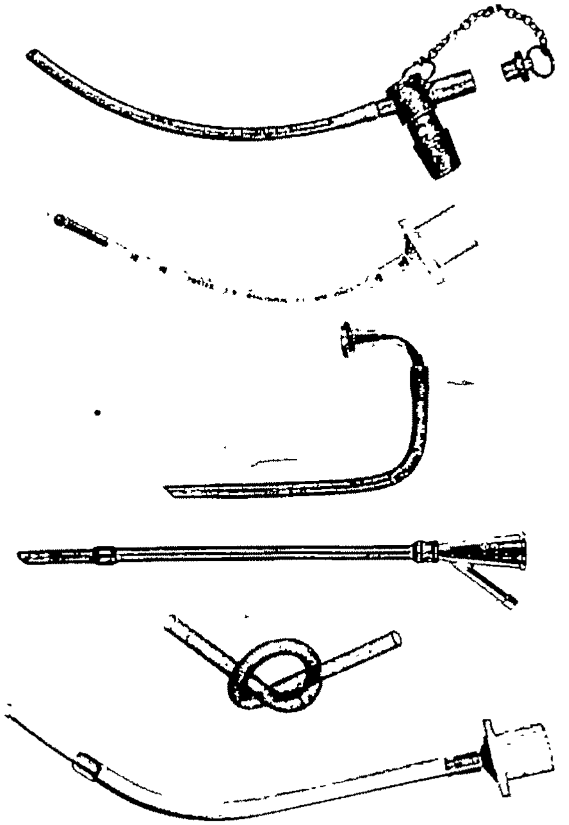

FIG. 5. Tracheal tubes commonly used in paediatric anaesthesia (from top downwards): Re-usable rubber Magill (with Cardiff connector); disposable plain tube; Oxford; Magill armoured; Latex armoured; Cole pattern. (From Hatch (1981).)

tubes are now implantation-tested, which removes one of their main disadvantages, but since they are more difficult to produce accurately than polyvinyl chloride (PVC) tubes, wall thicknesses vary more from tube to tube within the fairly wide tolerances allowed by Standards Organizations. Internal and external diameters, which are now marked on all tubes, should be checked before use, especially for neonates. Rubber tubes are more rigid than PVC ones, which makes them slightly easier to pass. For prolonged intensive care use, PVC tubes are used virtually exclusively, often by the nasal route.

A range of non-kinking tubes is available for paediatric use. The Oxford tube (fig. 5) is made of rubber, and the wall thickness and external diameter gradually increase from tracheal to machine end. Great care must be taken not to use too large a tube, as this will distend the larynx as it is passed. These tubes are slightly more difficult to pass than plain tubes, and the posteriorly facing bevel at the tracheal end can obstruct against the posterior wall of the trachea if the tube is pushed posteriorly or the head flexed. The pre-formed Rae or CAT tubes (fig. 6) can often be used as alternatives, although these may become compressed against the lower teeth by the tongue-plate of a mouth gag during pharyngeal surgery. Suction may be difficult through the CAT tube.

The Magill armoured flexometallic tube (fig. 5) is a rubber tube containing a spiral wire reinforcement within its main length, which is connected to the built-in connector. It is important to check that the rubber is firmly secured to this connection, as otherwise traction can cause the wire spiral to unfold and an uncorrectable leak to

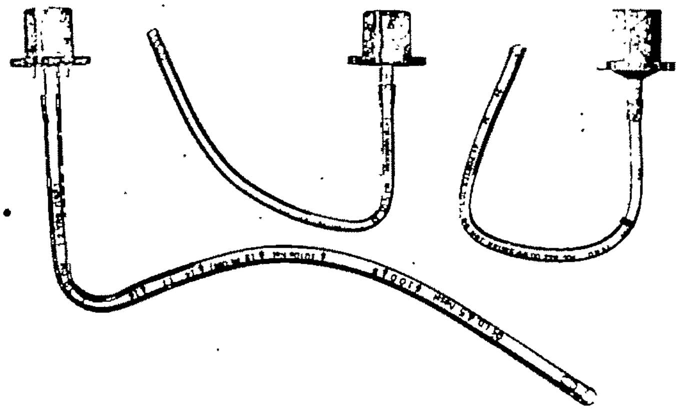

FIG. 6. Preformed disposable tracheal tubes: Rae pattern with Murphy eye (two, left); Childs anatomical tube (CAT) (right).

develop. The fresh gas inlet is seldom used. The tracheal portion is non-armoured and separated from the reinforced portion by a small area of increased external diameter. This is designed to prevent bronchial intubation, but passage of the wider section through the larynx with subsequent difficulty in extubation has been reported. However, the tube remains popular in many centres, particularly for neurosurgery. The latex armoured tube (fig. 5) can be used as an alternative in older children, both cuffed and non-cuffed versions being available. Wall thickness is too large for use in infants. Repeated sterilization tends to soften the latex and increase the risk of obstruction.

The Cole pattern tube (fig. 5) (Cole, 1945) was designed to reduce resistance by limiting the narrow laryngeal section to a short length of the terminal portion of the tube. Unfortunately, however, turbulent flow occurs at the area of sudden change in diameter (Hatch, 1978), so that resistance is not significantly different from uniform-bore tubes of similar external diameter with appropriate connectors attached. The tube has been popular with neonatologists because of the relative ease with which it can be passed, but long-term use has resulted in laryngeal damage from the pressure of the shoulder on the vocal cords, and its use is decreasing.

Whatever tracheal tube is used, it should be remembered that it is the site of most of the resistance to breathing. Thus, the largest tube which passes comfortably into the trachea should be used, whilst still allowing a small audible leak of gas around it during positive pressure ventilation, to avoid subglottic damage. In the neonate and young infant, in whom the smallest tubes are used and resistance highest (Cave and Fletcher, 1968), anaesthesia is usually accompanied by positive pressure ventilation.

A number of formulae have been devised for determining tracheal tube size (Keep and Manford, 1974; Penlington, 1974; Levin, 1980). Mostafa (1976) showed that there was considerable variation in tube sizes required at each age, and these formulae should be used only as a rough guide. They are not valid during the neonatal period or during most of the first year of life. The larynx of the full term neonate can usually accommodate a 3.0- or 3.5-mm tube (Fisher, 1983); infants weighing less than 3.5 kg usually tolerate a 3.0-mm tube (Thiebault and Nelson, 1979). In infants weighing less than 1.5 kg, a 2.5-mm tube is usually recommended. Gregory's recommendations for tube size may be helpful (table I), but at least three different sizes of tube should be available for each patient.

TABLE I. *Recommendations for tracheal tube size and type (from Gregory (1983))*

Age	Tube size (mm i.d.)	Type
Premature infant	2.5–3.0	Uncuffed
Term infant	3.0–3.5	Uncuffed
3 months–1 yr	4.0	Uncuffed
2 yr	4.5	Uncuffed
4 yr	5.0	Uncuffed
6 yr	5.5	Uncuffed
8 yr	6.0	Cuffed or uncuffed
10 yr	6.5	Cuffed
12 yr	7.0	Cuffed

Simple formulae which may be helpful for determining tube length are:

$$\text{Oral tube } \frac{\text{Age (yr)}}{2} + 12 \text{ cm}$$

$$\text{Nasal tube } \frac{\text{Age (yr)}}{2} + 15 \text{ cm}$$

but clinical assessment must be used to prevent bronchial intubation.

LARYNGOSCOPES

Because of the anterior, highly placed larynx in the infant, with the large soft epiglottis tending to obscure the laryngeal inlet, a straight-bladed laryngoscope is usually required up to 12–18 months of age. A variety of shapes of infant blade are available (fig. 7) and choice is largely a matter of personal preference. Many of these blades are now becoming available with a fibreoptic light source, which increases reliability in addition to improving the intensity of the illumination. The Seward or Robertshaw blades are particularly useful for nasotracheal intubation as they allow Magill forceps to be introduced to the mouth with minimum loss of view. The lightweight handle of the Anderson–Magill laryngoscope, with its hook for the index finger, is easy to hold, but the original light source was unreliable. Most of these blades can be used in the classical Magill fashion, with the tip placed posterior to the epiglottis or as for a Macintosh blade in the vallecula. The Macintosh blade is entirely satisfactory in most older children

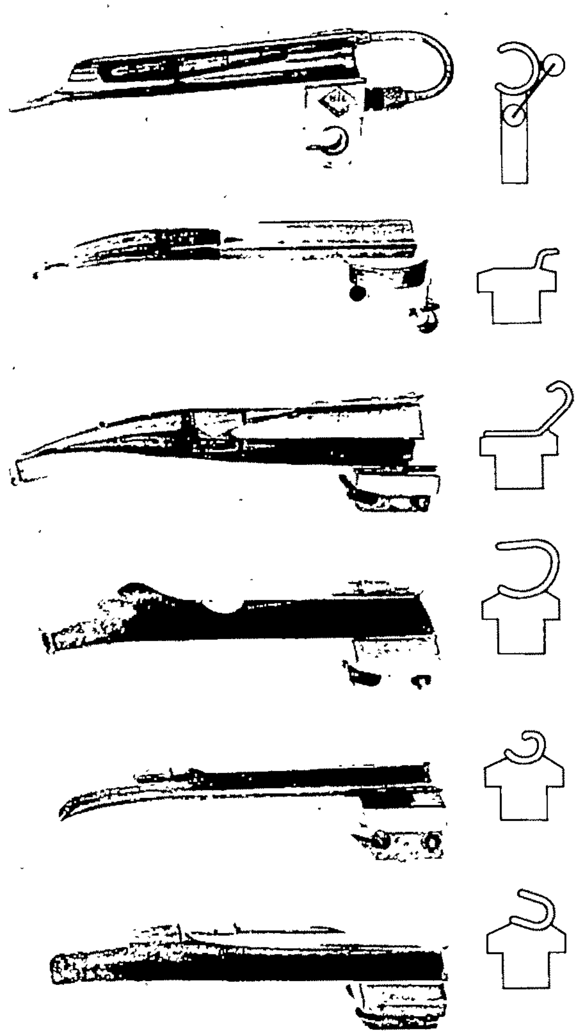

FIG. 7. Straight laryngoscope blades for use in infancy (from top downwards): Anderson–Magill; Seward; Robertshaw; Oxford; Miller; Wisconsin. (From Hatch (1981).)

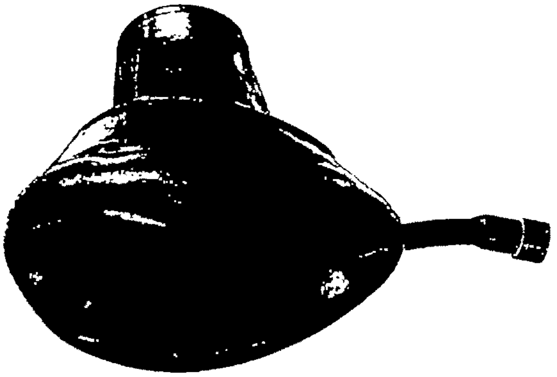

FIG. 8. Inflatable rimmed facemask. (From Hatch and Sumner (1981).)

and although a paediatric version is available, it has been found by many to be less convenient than the full-size adult blade. Moulded plastic laryngoscopes are useful for resuscitation purposes.

The fibreoptic bronchoscope and laryngoscope have been of considerable value as aids to difficult intubation in older children (Salem, Mathrubhutham and Bennett, 1976). The 3.2-mm instrument threads through a 4.5-mm tracheal tube (Rucker, Silva and Worcester, 1979). Following topical analgesia, the tube is passed nasally into the nasopharynx and the scope threaded through it and on into the trachea. Since it may cause significant airway obstruction in a small child, the tracheal tube should be threaded over it without delay. The instrument has also been used to facilitate nasotracheal intubation via the opposite nostril in a neonate with congenitally fused jaws (Alfery et al., 1979) or to aid intubation in an infant by first passing a cardiac catheter guide wire through the suction port of the adult bronchoscope (Stiles, 1974).

FACEMASKS

Facemasks are seldom used now for induction of anaesthesia, as induction is usually either i.v. or by inhalation from a gas inflow tube skilfully concealed in the anaesthetist's hand. However, they are sometimes required for preoxygenation, when the use of a clear plastic mask may be less frightening than a conventional black one. Antistatic material must be used when explosive agents such as cyclopropane are administered. Masks with inflatable rims (fig. 8) provide a better seal around the mouth, making inflation of the lungs easier, at least in inexperienced hands, and despite their relatively high deadspace are very useful for resuscitation purposes. Deadspace is reduced to some extent by channelling of gas flow within the mask.

The Rendell-Baker–Soucek facemask (fig. 9) is designed to provide a contoured fit around the infant's face, with reduction of deadspace to approximately 4 ml for the smallest size (Rendell-Baker and Soucek, 1962). The use of the partitioned facemask adaptor described by the

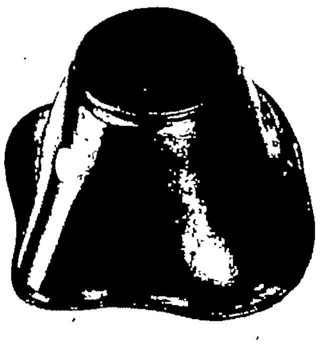

FIG. 9. Rendell-Baker–Soucek facemask. (From Hatch and Sumner (1981).)

same authors ensures that the fresh gas is carried down into the facemask and reduces apparatus deadspace still further. The Keats and Hustead elbows act in a similar fashion. Since tracheal intubation is performed in most neonatal anaesthetics, the subject of mask deadspace is less important than it appears at first sight. A little practice is required before the Rendell-Baker–Soucek mask can be used for inflating the lungs without leaks occurring between the mask and the face.

PHARYNGEAL AIRWAYS

The Guedel airway is now used virtually universally and is available in five sizes from 2 to 000. Neonates sometimes require a larger airway than expected.

INTRAVENOUS EQUIPMENT

For the induction of anaesthesia in infants and small children, sharp fine needles are required, and these are now available in gauges as small as 27 s.w.g. Scalp vein type needles have wings which can be used to fix the needle down after insertion, and are useful for intermittent injections. However, they should not be relied upon for fluid replacement during major surgery and care should be taken when injecting irritant drugs, as even in careful hands they may easily cut out of the vein. Fortunately there is now a wide range of i.v. cannulae available in sizes as small as 26 s.w.g., and made of a variety of synthetic plastic materials such as "Teflon" with a low frictional resistance. These cannulae can be used for peripheral venous, central venous and arterial cannulation at all ages, using percutaneous techniques.

Cannulae should be fixed securely and it is wise to interpose a short length of narrow-bore extension tubing between the cannula and a three-way stopcock to minimize any interference with the cannulation site. Whenever possible, Luer lock connections should be made, and this is essential with central venous cannulae if air embolism is to be avoided.

When very accurate volumes of fluid are to be administered, it is wise to use a syringe and three-way stopcock. Accurate infusions should be given using either an electronically controlled gravity feed giving set or an infusion pump. If the latter is used the cannulation site should be checked regularly for extravasation to the tissues. When accuracy of volume administration is less critical, a standard paediatric burette with 30–100 ml chamber is adequate. When blood is administered rapidly or in large volumes it should be warmed and filtered as for an adult. Blood loss should be carefully measured using scales for swab-weighing and surgical suction apparatus which allows small volumes of blood to be measured accurately.

APPARATUS TO PROVIDE HEAT

Infants are particularly susceptible to heat loss because of their large surface area to weight ratio, poor subcutaneous insulation and immature thermogenic mechanisms. Attempts to generate heat by the metabolism of brown fat stores are inhibited by general anaesthesia and also by acidosis and hypoxia. It is essential, therefore, that steps are taken to minimize heat loss at all times, but especially during surgery. Whilst keeping the infant covered, increasing the operating theatre temperature and wrapping the head and limbs in silver foil all help to conserve heat, these steps are seldom adequate on their own and some apparatus is required to provide an external heat source. For many years, this has been either an electric or water-filled blanket placed under the infant, but both these pieces of apparatus have serious disadvantages. Electrical burns have been reported from electric blankets following thermostat failure. Water blankets are cumbersome and inefficient, and often leak or are punctured by surgical towel clips. Both these forms of heating have the additional limitation of only providing heat by conduction at the point of contact with the infant.

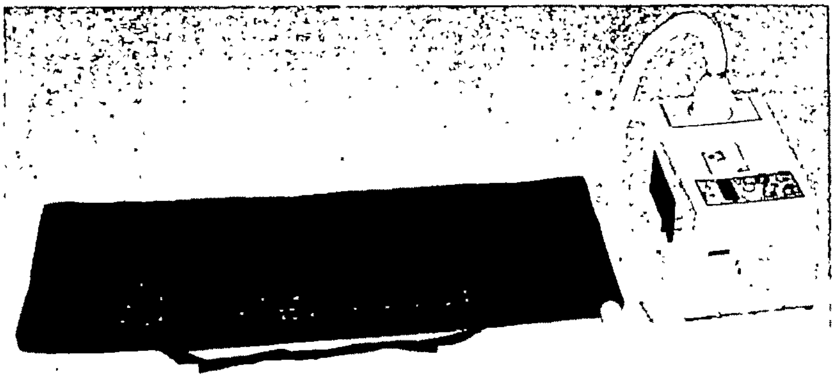

FIG. 10. Hot air mattress and pump for operating theatre use.

In recent years, a circulating hot-air mattress has been described which is safer and more efficient (fig. 10). Air is blown from a pump through channels in a foam mattress, which is covered with Gortex so that air can flow through it whilst it remains impermeable to fluids. The hot air permeates the surgical drapes so that the infant receives heat by convective currents surrounding him in addition to heat by conduction. Using this system, it has been found that other methods of heat supply, such as warming the inspired gas, are unnecessary.

VENTILATORS

The use of ventilators with the T-piece or Bain systems has been described above. Other ventilators can be used satisfactorily in small children, but they must be capable of delivering tidal volumes as small as 10 ml, at respiratory frequencies between 20 and 60 b.p.m. It is also useful to be able to adjust the inspiratory flow rate and inspiratory:expiratory ratio so that peak airway pressures can be kept as low as possible. Occasionally, peak pressures up to 7 kPa may be required. For use during surgery, there must also be a manual system and the ability to flush the apparatus with oxygen, in addition to provision for anaesthetic gases. Although many of the sophisticated ventilators used for paediatric intensive care can be used in the operating theatre, this degree of sophistication is not really necessary, and the complex array of knobs, switches and alarms may in fact be a disadvantage. Several simpler systems have been described which are satisfactory, including conversions from adult machines (Inkster and Pearson, 1967). It must be remembered that the volume of gas leaving the machine is considerably greater than that reaching the patient, because of the amount lost in compression in the tubing of the breathing system. With adult ventilators, the compression volume is often as large as 0.45 ml kPa^{-1} (Robbins, Crocker and Smith, 1967). With a peak inflating pressure of 2 kPa (20 cm H_2O), 90 ml is lost in compression per breath, which represents considerably more than the tidal volume required by the average neonate. Provided that this factor is allowed for, adequate ventilation can still be obtained, although changes in compliance and resistance lead to marked changes in gas lost in compression and hence in tidal volume. Epstein and Hyman (1980) have described a ventilator (with a compressible volume as low as 0.003 ml kPa^{-1}) which delivers a constant tidal volume despite changes in lung mechanics, but in all other ventilators manual readjustments must be made. Changes in compliance and resistance also affect the amount of gas which leaks around the tracheal tube, and this further complicates the situation.

MONITORING EQUIPMENT

Meticulous cardiovascular, respiratory and temperature monitoring are essential in paediatric anaesthesia, and a wide and confusing range of

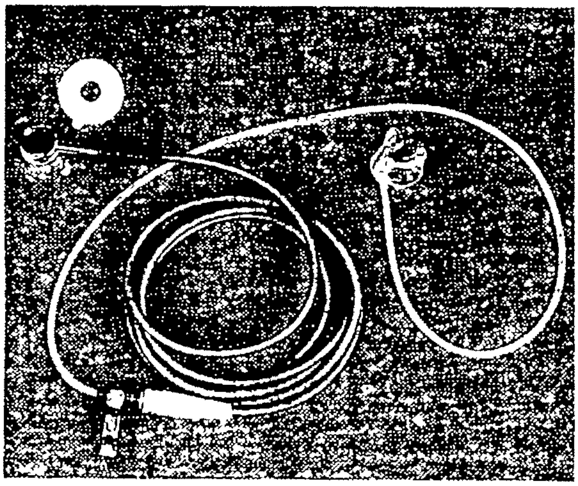

FIG. 11. The precordial stethoscope with moulded earpiece.

equipment is now available to help the anaesthetist. Although much equipment is sophisticated and expensive, some of the simple items such as the precordial stethoscope (fig. 11) remain among the most valuable. When used in conjunction with a moulded mono-aural earpiece, which can usually be obtained from hospital hearing-aid departments, this becomes a continuous and reliable monitor of respiration and cardiac impulse. Any airway problem such as disconnection or obstruction is likely to be noticed immediately, as are changes in heart rate. It is even possible to gain a little information on cardiac output from the quality of the heart sounds. In older children the oesophageal stethoscope serves the same purpose.

Cardiovascular monitoring equipment

In addition to the precordial stethoscope, ECG and arterial pressure recording devices should probably always be used during paediatric anaesthesia, and their use becomes mandatory during major operations and those where significant blood loss is expected. Digital display of heart rate allows rapid assessment of changes and is a major step forward in cardiovascular monitoring, but the ability to recognize even minor arrhythmias, enabling steps to prevent progression to more serious rhythms, is also of fundamental importance. Most modern machines have clear displays and have overcome the problem of electrical interference from surgical diathermy.

The modern generation of automatic recording arterial pressure devices is rapidly replacing previously favoured methods such as the Doppler ultrasound. It must be remembered, however, that arterial pressure can change very rapidly and the displayed results represent the values when measured and not the current situation. Too frequent inflations may lead to oedema or petechial haemorrhages in the limb. These devices have been shown to be less accurate at extremes of arterial pressure (Hutton, Dye and Prys-Roberts, 1984) and it is important to remember that infants and young children have normal values different from those in adults (Gregory, 1983).

Direct arterial cannulation is advisable for the most major surgical procedures, including cardiac and much neurosurgery, and also in any sick infant or child, especially when postoperative cardiorespiratory disturbances are expected, such as congenital diaphragmatic hernia or necrotizing enterocolitis.

Respiratory monitoring equipment

As noted above, the precordial stethoscope is extremely valuable for monitoring breath sounds, but until recently there have been few other pieces of apparatus available for respiratory monitoring. In recent years, a number of monitors of thoracic or abdominal excursion have become available, the most convenient for use in the operating theatre using changes in impedance. Whilst these devices may be of value during controlled ventilation, they often fail to detect apnoea during spontaneous breathing, probably because of the artefact created by the heart beat impulse (Southall et al., 1983). In addition, monitoring of end-tidal carbon dioxide has become much more frequent with the development of capnographs which are easy to use as clinical monitors as opposed to research instruments. It is now possible to measure carbon dioxide using an infra-red analysing head placed across a small glass window in a cuvette placed in the breathing system (fig. 12A). The smallest cuvette (fig. 12B) has a deadspace of 2 ml and response time of 0.02 s, making it suitable for neonatal use. Capnographs which require a sample of expired gas should have a sample flow rate of approximately 60% of the tidal volume per minute. Higher sample flow rates may entrain inspired air (Gregory, 1983).

Tidal and minute volumes have always been difficult to measure in children, but the recently introduced "Infanta" version of the Wright respirometer can record volumes down to 15 ml. Its resistance is 0.24 kPa litre^{-1} s^{-1} at 15 litre min^{-1} and its deadspace has been reduced to 15 ml. If

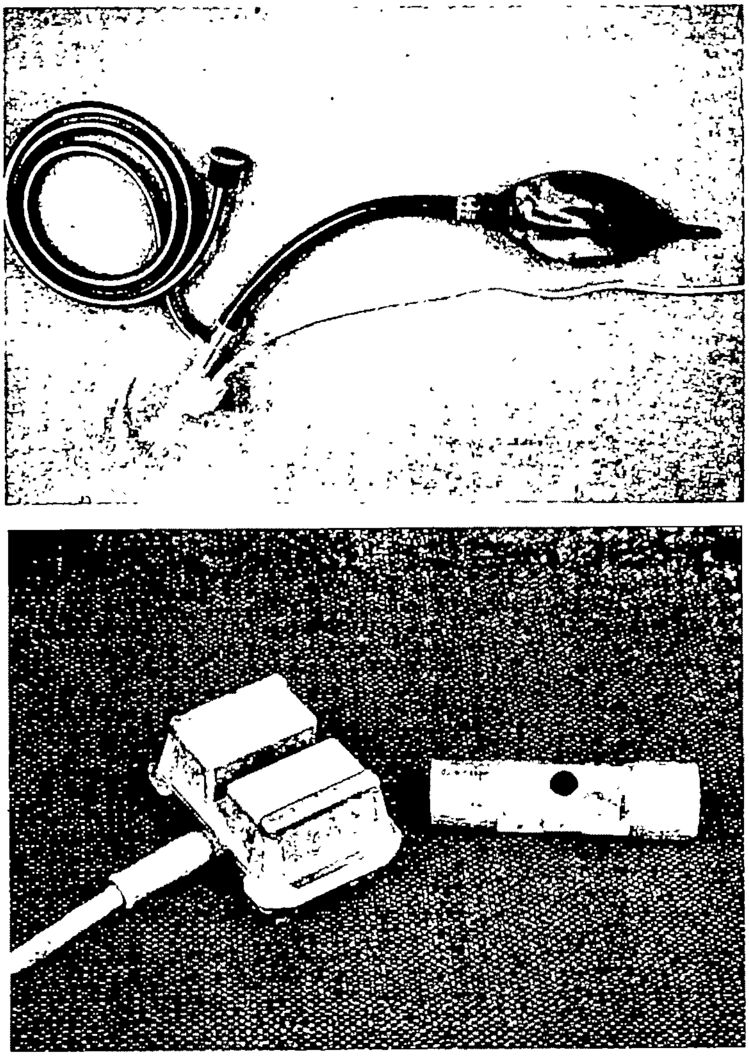

FIG. 12. A (above): Capnograph cuvette placed within the deadspace of a T-piece breathing system.
B (below): Infra-red capnograph head with paediatric cuvette.

placed between the Nuffield 200 ventilator and the T-piece during controlled ventilation, it can act as a useful teaching aid in relation to the behaviour of the breathing system, in addition to providing a monitor of ventilation (fig. 13).

In recent years there has been increasing interest in the use of transcutaneous oxygen and carbon dioxide electrodes during anaesthesia, particularly in preterm infants who are susceptible to retrolental fibroplasia if exposed to high oxygen tension in the retinal vessels. Transcutaneous oxygen tension ($P\text{tc}_{O_2}$) measurements are used widely in neonatal intensive care, but have not been used so often during surgery. This may result partly from the effect of halothane and nitrous oxide on their accuracy, since both these agents are reduced by the electrode, causing a false increase of $P\text{tc}_{O_2}$. This effect has been overcome, however, in more recent electrodes, either by offsetting the applied voltage or by changing the electrolyte (Thunstrom and Severinghaus, 1978). When peripheral perfusion is satisfactory, there is good correlation between $P\text{a}_{O_2}$ and $P\text{tc}_{O_2}$ at values up to 13.3 kPa, although above this value $P\text{tc}_{O_2}$ measurements tend to be low in relation to $P\text{a}_{O_2}$. Good correlation also exists between $P\text{a}_{CO_2}$ and $P\text{tc}_{CO_2}$,

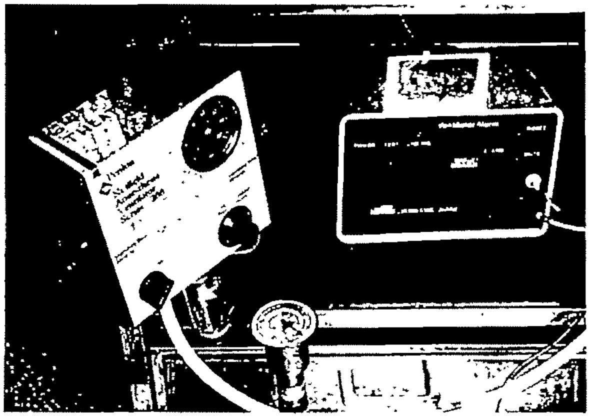

FIG. 13. The "Infanta" Wright respirometer in use with the T-piece and Nuffield 200 ventilator. When placed in this position, it acts as an aid to the diagnosis of disconnection or airway obstruction. Inspiratory flow increases following disconnection and decreases with obstruction. To monitor tidal volume, a simple calculation of the contribution made by the fresh gas flow (FGF) must be carried out: (FGF s^{-1})/(inspiratory time).

although the transcutaneous value is increased by cutaneous carbon dioxide production, for which a correction is necessary. Ptc_{O_2} values decrease dramatically with reductions in peripheral perfusion, and increasing heat output by the device in the face of decreasing skin temperature has been correlated with declining arterial pressure.

A continuously recording catheter-tip electrode has been developed for the measurement of oxygen tension in the umbilical artery (Parker et al., 1971), and continuously recording tissue pH probes have also become available (Filler and Dao, 1971), but their place in anaesthetic practice is unclear at present.

Temperature monitoring equipment

Because of the increased liability of infants to lose heat in a cold environment, accurate monitoring of temperature is extremely important. Some form of electrical thermometer, usually a thermistor, is used to record, usually, from the nasopharynx, oesophagus or rectum. Suitable small atraumatic probes are required, and those used in veterinary practice are often suitable.

SUMMARY

Paediatric anaesthesia is made easier and safer by use of the correct equipment. The widening range and increasing complexity of available apparatus makes it essential for the anaesthetist to judge which items are most useful in any individual case. As a general rule, the simplest pieces of equipment are the most reliable and among the most useful.

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SCAVENGING EQUIPMENT

W. M. GRAY

REASONS FOR SCAVENGING

The widespread introduction of scavenging systems during the past decade is a result of the growing realization that chronic exposure to trace concentrations of anaesthetic gases may constitute a health hazard to operating theatre personnel. On the basis of epidemiological studies carried out since the mid 1960s, it has been suggested that operating theatre staff and their wives and children are subject to an increased risk of various pathologies, including spontaneous abortion, stillbirth, congenital abnormalities, low birth weight, altered sex ratio, infertility, cancer, liver disease and kidney disease. These reports have prompted several investigations into whether or not anaesthetic agents are fetotoxic or carcinogenic in animals, but these have yielded conflicting results. Vessey and Nunn (1980) have critically reviewed both the epidemiological and the animal studies, and conclude that, while the evidence for most of the above hazards is unconvincing, the increased risk of abortion in female theatre staff is reasonably well substantiated. Furthermore, two of the studies that they reviewed (Cohen et al., 1980; Lane et al., 1980) strongly suggest that high concentrations of nitrous oxide may be the causative factor. This interpretation is supported by recent reports that exposure of pregnant rats to trace concentrations of nitrous oxide produces adverse effects on their fetuses (Vieira et al., 1980; Vieira, Cleaton-Jones and Moyes, 1983).

A possible mechanism for the fetotoxic effects of nitrous oxide has recently been described. Nitrous oxide inhibits the enzyme methionine synthase by inactivating its bound co-factor methyl cobalamin (a form of vitamin B_{12}), and this action has major metabolic consequences; one of these is the impairment of deoxyribonucleic acid synthesis, which could well produce fetotoxic effects (Sharer et al., 1983).

As a result of the increasing concern about the possible hazards of exposure to waste anaesthetic gases, the Association of Anaesthetists of Great Britain and Ireland (1975) has recommended that all anaesthetizing locations should be equipped with scavenging systems, and this is now official DHSS policy (Department of Health and Social Security, 1976).

TARGET LEVELS FOR OPERATING THEATRE POLLUTION

In the U.K., no official limit has been set for the safe maximum exposure to waste anaesthetic gases. Instead, the Department of Health and Social Security (1976) has recommended that pollution "should...be reduced as far as is practically possible". However, some guidance on target concentrations can be obtained from the recommendations published in the U.S.A. by the National Institute for Occupational Safety and Health (NIOSH) (1977), which are that average personnel exposures during anaesthetic administration should not exceed 25 p.p.m. for nitrous oxide and 2 p.p.m. for any halogenated agent. Sharer and colleagues (1983) have criticized the NIOSH limit for nitrous oxide as being too restrictive, and have suggested a limit of 200 p.p.m., based on a consideration of the data on methionine synthase inactivation and fetotoxicity. It seems likely that any future statutory limit for nitrous oxide exposure will be higher than the NIOSH limit, and not less than 100 p.p.m.

EFFICACY OF SCAVENGING

The introduction of scavenging techniques can reduce pollution by 90% or more (Oulton, 1977; McIntyre, Purdham and Hosein, 1978; Davenport

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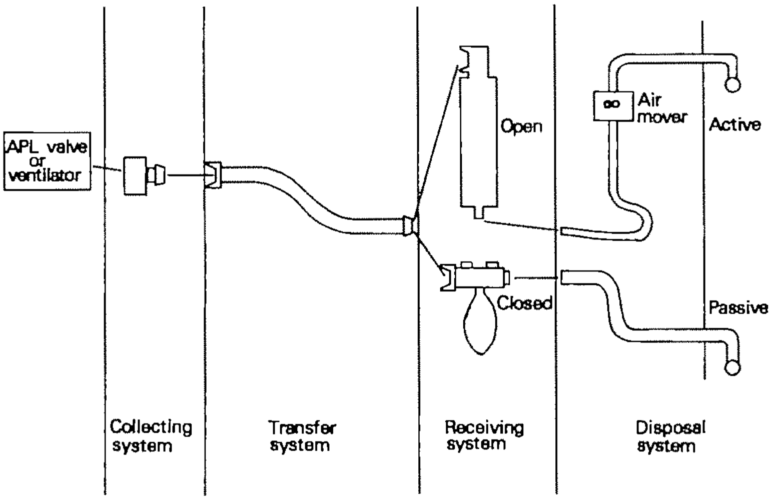

FIG. 1. Schematic diagram of scavenging system, showing alternative types of receiving and disposal systems.

et al., 1980; Krapez et al., 1980). However, scavenging will be as effective as this only if great care is taken to minimize leaks from the anaesthetic equipment and if a "clean" anaesthetic technique is used (Berner, 1973; Lecky, 1977; McIntyre, Purdham and Hosein, 1978; Krapez et al., 1980). In addition, because some spillage of anaesthetic gas is unavoidable, it is necessary to have an effective theatre ventilation system to achieve acceptably low concentrations of atmospheric contamination (Langley and Steward, 1974; Piziali et al., 1976; Halliday et al., 1979).

DEFINITIONS AND STANDARDS

An *anaesthetic gas scavenging system* is a system that collects excess anaesthetic gas from the breathing system and discharges it outside the working environment. A complete system consists of four parts, as shown in figure 1. The excess gas is gathered in a *collecting system*; it is transported through a *transfer system* to a *receiving system*, which protects the patient against excessive positive or negative pressure* and usually provides some reservoir capacity; finally the gas is removed by a *disposal system* to a safe place of discharge. The collecting, transfer, receiving and disposal systems may be designed and built as separate sub-systems; alternatively, any one system may be integrated with one or more of the others or with associated equipment, such as an anaesthetic machine or automatic ventilator.

A variety of alternative names has been used for each component of a scavenging system (Dorsch and Dorsch, 1984). The terminology used above is that used in the draft British Standard on scavenging equipment (British Standards Institution, 1983). This document provides specifications for performance and patient safety, which incorporate and amplify the advice given by the Association of Anaesthetists of Great Britain and Ireland (1975) and the Department of Health and Social Security (1976). In the U.S.A., the American National Standards Institute (1982) has published a standard for anaesthesia gas pollution control. Hereafter, these documents will be referred to as the "draft BS" and the "ANSI standard".

PATIENT SAFETY

Hazards

The relationship between scavenging systems and patient safety has been expressed clearly by Lecky (1977) as follows: "Scavenging equipment in an anaesthetic system adds complexity, and thus hazards, to the administration of anaesthesia. A scavenging system extends the anaesthetic circuit all the way to the ultimate disposal point, so that any pressure alterations brought about by unopposed vacuum in or blockage of the scavenging system can be transferred to the anaesthesia circuit, potentially harming the patient. For safety, then, the most important component of an excess gas scavenging system is the interface, designed to relieve positive pressure in the event of scavenging system occlusion and to prevent vacuum pressures from reaching the patient circuit when a blower or central suction system is used for excess gas elimination." The "interface" referred to is what is termed the "receiving system" in this paper.

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* In this paper, the established practice is used of taking atmospheric pressure as the origin for pressure measurements, so that pressures greater than atmospheric are regarded as positive and pressures less than atmospheric as negative.

Several incidents in which excessively high pressure has been transmitted to the breathing system because of obstruction of the scavenging system have been reported. The causes of obstruction included: occlusion of the disposal system by a wheel of an anaesthetic machine (Davies and Tarnawsky, 1976; Tavakoli and Habeeb, 1978; Mantia, 1982); incorrect assembly of a component in the disposal system (Hamilton and Byrne, 1979); and blockage of the disposal tubing with ice (Hägerdal and Lecky, 1977). In none of these instances was a positive pressure relief device included in the scavenging circuitry.

Incidents have also been reported in which dangerously high pressure developed in a circle system because the expiratory tubing of the system was accidentally connected to the exhaust port of the adjustable pressure limiting (APL) valve rather than to the expiratory port on the carbon dioxide absorber (Tavakoli and Habeeb, 1978; Flowerdew, 1981; Mann and Sprague, 1982). These incidents illustrate the need for scavenging equipment to be so designed that its components cannot be interconnected with those of the breathing system.

The dangers of applying unopposed vacuum to the breathing system were described by Sharrock and Leith (1977), who investigated the effects of such an insult on three types of APL valve and found that two of the valves transmitted the suction to the breathing system while the third (a diaphragm valve) was closed by the suction, causing the pressure in the breathing system to increase. To circumvent this hazard, they recommended that scavenging equipment should include a negative pressure relief valve, and stressed that such a valve must be designed carefully and checked regularly in order to be effective. The aptness of this advice was soon demonstrated by reports of incidents of the type which Sharrock and Leith sought to warn against. In some instances, excess suction was transmitted to the breathing system (Mor, Stein and Orkin, 1977; Abramowitz and McGill, 1979; Patel and Dalal, 1979), while in others, involving a diaphragm APL valve, the pressure in the breathing system increased (Malloy et al., 1979; Rendell-Baker, 1982). In all of these incidents, a mechanism for negative pressure relief was included in the scavenging system, but failed because of poor design, inadequate maintenance or careless use.

Requirements

The draft BS on scavenging equipment includes the following provisions for patient safety:

(1) At a continuous flow of air 30 litre min^{-1}, the scavenging system should not impose a greater resistance than 50 Pa.

(2) In the event of total obstruction of the system, or failure of the power supply, the resistance should not be greater than 1 kPa at a flow of 30 litre min^{-1}. If the transfer tubing is less than 1 m in length, the necessary pressure relief may be afforded by the receiving system.

(3) The scavenging system shall not create a sub-atmospheric pressure in the collecting system of more than 50 Pa.

Point (3) requires some comment. It has been realized recently that sub-atmospheric pressures of less than 50 Pa can produce potentially hazardous effects in breathing systems as the result of flow induction; examples are the evacuation of a paediatric breathing system (Houghton and Taylor, 1983), the defeat of a ventilator disconnection alarm (Gray et al., 1984) and the activation of a ventilator's negative end-expiratory pressure mechanism (Goudie, 1984). It therefore seems likely that the final British Standard will impose more stringent requirements on permissible sub-atmospheric pressure.

The draft BS also contains other safety provisions, including measures to prevent accidental misconnection between the scavenging system and the breathing system. These will be described in the following sections.

COLLECTING SYSTEM

To avoid accidental misconnection between breathing system and scavenging system components, the outlet fitting of the collecting system should be incompatible with the breathing system connections, which have been standardized to 22-mm and 15-mm conical fittings (British Standards Institution, 1965). Both the ANSI standard and the draft BS specify a male conical fitting, of 30-mm or 19-mm diameter, for the collecting system outlet. However, it seems likely that the final British Standard will allow only a 30-mm fitting.

The design of the collecting system depends on the type of anaesthetic system with which it is to be used. (The breathing systems referred to below are described by Conway (1982, 1985).)

Breathing systems without a ventilator

Systems with APL valve. These include the circle system and the Mapleson A, B, C and D systems. The basic APL valve is replaced by a valve with identical function, but fitted with a shroud, which constitutes the collecting system (fig. 2). (Note that the APL valve itself is a component of the breathing system, not of the scavenging system.) The use of a breathing system in which the APL valve can be attached to the anaesthetic machine avoids the need for the transfer tubing to stretch to the patient's face. Thus, the circle system, the Lack variant of the Mapleson A system and the Mapleson D system (including the Bain variant) are more convenient to use with scavenging than the standard Mapleson A, B and C systems.

Hafnia Systems. The design of these systems is based on the concept of controlled removal of the waste gases, and the systems do not have a physically separate collecting system. Indeed, a Hafnia system can be considered as an integrated breathing, collecting and receiving system.

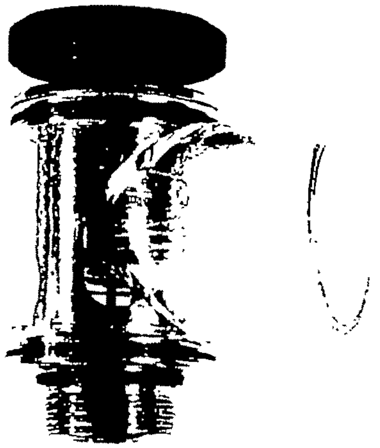

FIG. 2. Shrouded APL valve with 30-mm male conical outlet. (Manufactured by Penlon Ltd, a member of the InterMed Group.)

Systems with non-rebreathing valve. A non-rebreathing valve fitted with a scavenging port is now commercially available, and other non-rebreathing valves can often be fitted with a collecting device without adverse effect on their function (Dorsch and Dorsch, 1984).

T-Piece systems without an APL valve (Mapleson E and F systems). Most of the scavenging devices for these systems that have been described (Cestone, Ryan and Loving, 1976; Brinkløv and Andersen, 1978; Flowerdew, 1979; Houghton and Taylor, 1983) involve the physical attachment of the collecting system (in some cases integrated with the receiving system) to the end of the T-piece, with a consequent and undesirable increase in resistance to breathing. However, Hatch, Miles and Wagstaff (1980) have described a system which avoids this problem: the waste gases from the T-piece are directed towards a scavenging dish and entrained in a large flow of room air drawn through the dish by the disposal system. The dish thus acts as a combined collecting and receiving system.

Breathing systems with a ventilator

In such an arrangement (Dorsch and Dorsch, 1984), the APL valve is closed, and all waste gas is discharged from the ventilator. Some older models of ventilator are difficult to scavenge effectively, and many ventilators had to be totally redesigned in order to allow efficient scavenging. Most modern ventilators are equipped with a gas-tight collecting system, or can be readily fitted with one, and some are supplied with a receiving system and disposal system fitted. In the case of ventilators fitted with only a collecting system, it is convenient to join the outlet from this system to that from the APL valve, to avoid the need to re-connect the transfer tubing upon changing from spontaneous to automatic ventilation. This connection can be made at the inlet to the receiving system (fig. 3).

Extracorporeal pump oxygenators

If gaseous anaesthetics are used with patients on cardiac by-pass, the outlet port of the oxygenator is a potential source of anaesthetic pollutants. Although several scavenging attachments (combined collecting and receiving systems) for oxygenators have been described (Annis, Carlson and Simmons, 1976; Miller, 1976; Muravchik, 1977), none has yet been fully developed (Dorsch and Dorsch, 1984). It is particularly important to provide adequate pressure relief in such attachments, since the performance of oxygenators is appreciably altered by pressure fluctuations.

TRANSFER SYSTEM

This normally consists of a length of tubing with a connector at either end. These connectors should be of a gauge different from that of the breathing system fittings and should be compatible with the outlet from the collecting system and the inlet to the receiving system. A 30-mm female inlet connector and a 30-mm male outlet connector would conform with both the ANSI standard and the draft BS requirements. The tubing should be kept as short as possible (this is facilitated by mounting the receiving system on the anaesthetic machine), and care should be taken to avoid kinking or otherwise occluding it. If the transfer tubing is longer than 1 m, the draft BS requires that additional positive pressure relief be provided adjacent to the collecting system. This can be achieved by fitting an additional valve between the collecting system and the transfer tubing, or by using an APL valve assembly that is modified to incorporate a relief valve (Gil-Rodriguez, 1984).

PERFORMANCE REQUIREMENTS FOR RECEIVING AND DISPOSAL SYSTEMS

In order to fulfil their intended function, the receiving and disposal systems must be able to accept the varying flow of waste gases from the breathing system without any spillage into the working environment. Spontaneously breathing patients have minute volumes of up to approximately 6 litre min^{-1} and peak flows of up to approximately 30 litre min^{-1}, whereas, with artificially ventilated patients, minute volumes of up to approximately 20 litre min^{-1} and peak flows of up to approximately 75 litre min^{-1} may be encountered (Nunn, 1977). Thus, the use of artificial ventilation imposes greater demands on a scavenging system than does spontaneous breathing. Moreover, the driving gas may be added to the waste anaesthetic gas, thus augmenting both the mean and peak flows. Thus, a scavenging system that can function efficiently with spontaneously breathing patients may fail to do so when used with some automatic ventilators (Railton and Fisher, 1984).

The draft BS specifies stringent performance requirements for receiving and disposal systems, which are intended to ensure that the systems function efficiently with all ventilators currently in use. It requires that the receiving and disposal systems should be capable of receiving, without spillage, an input made up by combining a continuous flow of air of 60 litre min^{-1} with an intermittent flow of a 50% nitrous oxide in oxygen mixture of 45 litre min^{-1}, superimposed on the continuous flow for 1 s in each successive 4-s period. In addition, it specifies that the disposal system should be capable of providing an extraction flow of 100–130 litre min^{-1} from each receiving system.

It should be stressed that a scavenging system may fail to fulfil these requirements, yet operate satisfactorily under most circumstances. Although such a system may not scavenge a "difficult" ventilator efficiently, the only ill-effect of this failure will be some contamination of the operating theatre atmosphere. Thus, the BS requirements should not be interpreted as an imperative to replace existing systems, but rather as a guide for new installations.

RECEIVING SYSTEM

The receiving system constitutes the main interface between the breathing system and the disposal system, and it fulfils the vital function of protecting the patient from excessive positive or negative pressures. In addition, it usually provides some reservoir capacity to ease the task of the disposal system in dealing with the peak expiratory flows from the breathing system.

The draft BS requires that the inlet to the receiving system should be a female 30-mm conical fitting. (A male 19-mm conical fitting is also allowed, but this clause is likely to be omitted from the final Standard.) Furthermore, any connectors fitted between the receiving system and the disposal system should not be compatible with the fittings in the breathing system or with those allowed between the collecting system and the transfer system; that is, not 15-mm, 22-mm, 19-mm or 30-mm conical fittings.

Receiving systems can be either *closed* or *open*. In a closed system, the reservoir is a distensible bag, of approximately 2-litre capacity, and pressure protection is provided by positive and

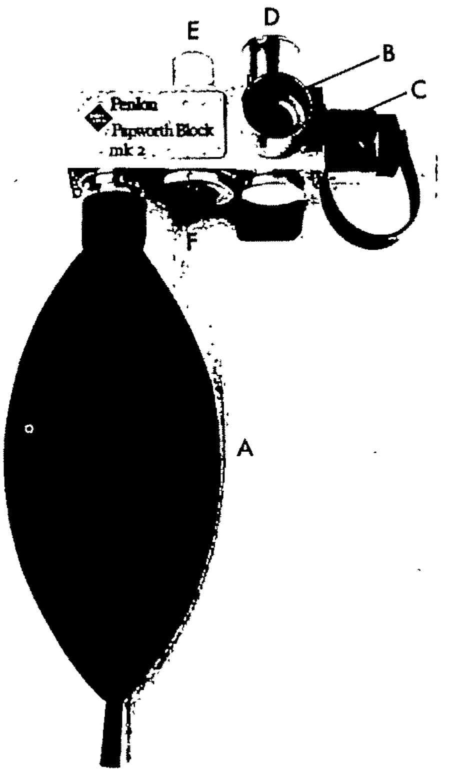

FIG. 3. Closed receiving system. A = reservoir bag; B = inlet for anaesthetic machine (30-mm female conical); C = inlet for ventilator (30-mm female conical); D = outlet to disposal system (32-mm hose push-on connector); E = positive pressure relief valve; F = negative pressure relief valve. (Courtesy of Penlon Ltd, a member of the InterMed Group.)

negative pressure relief valves (fig. 3). In an open system, pressure protection is provided by an air break between the connections to the transfer and disposal systems, and reservoir capacity by a length of tubing enclosing these connections at one end and open to atmosphere at the other end (fig. 4). (However, one commercially available open system has minimal reservoir capacity, and depends on a high disposal flow to prevent spillage (Mostafa and Natrajan, 1983).)

With a closed system, leakage of waste gases into the atmosphere can only occur if the reservoir bag becomes fully inflated and the pressure increases sufficiently to open the positive pressure relief valve. In contrast, the effectiveness of an open system in preventing spillage depends not only on the volume of the reservoir, but also on the behaviour of the oscillating interface between the

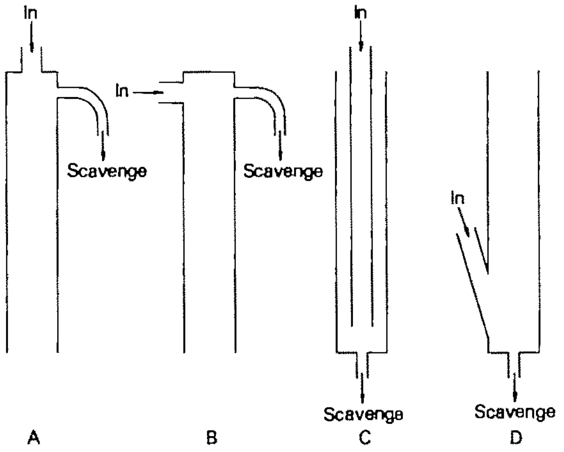

FIG. 4. Some different types of open receiving systems. A = top injection; B = cross flow injection; C = co-axial injection (tube-within-a-tube); D = oblique injection. (Redrawn for Houldsworth, O'Sullivan and Smith, 1983a).)

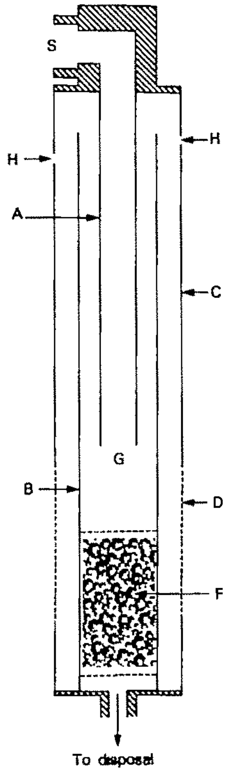

FIG. 5. Schematic diagram of Barnsley receiving system. A = inner tube; B = intermediate tube; C = safety sheath; D = gauze-covered venting slots; F = silencer packing; G = discharge point of inner tube; H = safety holes; S = 30-mm conical socket. (Reproduced from Houldsworth, O'Sullivan and Smith (1983b), with permission of the authors and publishers.)

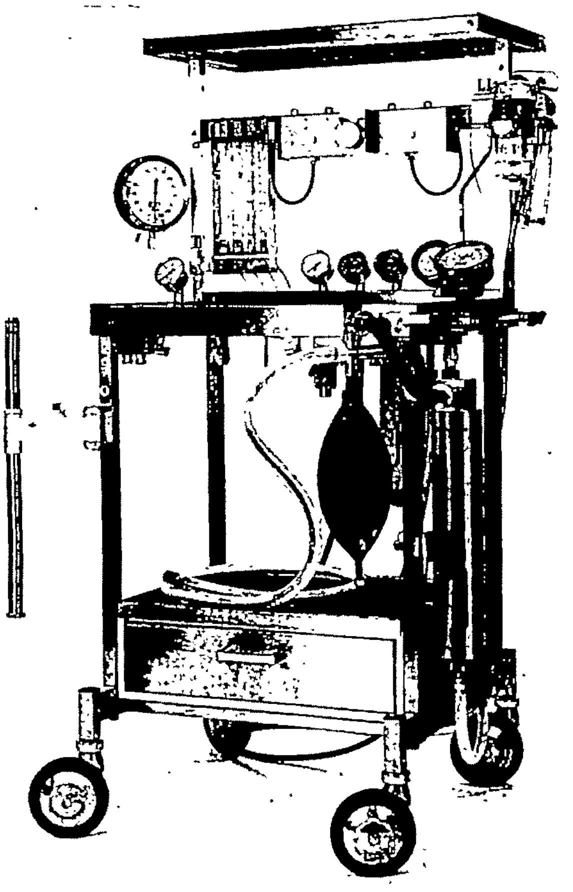

FIG. 6. Barnsley receiving system attached to anaesthetic machine and set up to receive waste gases from a Bain breathing system. (Courtesy of Dr H. B. Houldsworth.)

injected pollutants and the air in the reservoir (Houldsworth, O'Sullivan and Smith, 1983a). If large scale turbulence occurs at this interface, leakage into the atmosphere can occur well before the volume of waste gas injected to the receiving system equals the reservoir volume. The behaviour of the interface depends on the flow pattern of the injected pollutants, the disposal flow rate and the geometry of the receiving system. Houldsworth, O'Sullivan and Smith (1983a) investigated the scavenging efficiency of the different types of receiving system shown in figure 4 for a range of flow patterns and disposal flows, and found that the co-axial injection design consistently produced the least turbulence and hence afforded the greatest efficiency. Figures 5 and 6 show a commercially available receiving system incorporating the design features suggested by this investigation (Houldsworth, O'Sullivan and Smith, 1983b).

Closed receiving systems suffer from the disadvantage that the pressure relief mechanism relies on mechanical valves, which require regular checking to ensure that they operate smoothly. Furthermore, these valves can present a substantial resistance to gas flow (Brinkløv, Andersen and Jørgensen, 1978); therefore a closed system is not suitable for use with a high flow disposal system, which will usually draw a large fraction of its total flow through the negative pressure relief port of the receiving system and could consequently generate appreciable negative pressure within the reservoir. Instead, closed systems are better suited for use with low flow active disposal systems or with passive systems.

An open receiving system is the most suitable type for use with high flow disposal systems such as are specified in the draft BS. The degree of safety afforded by an open system is entirely dependent on the patency of the vents which constitute the air break to the atmosphere, and it is essential to have considerable redundancy in the provision of such passages in order to allow for the possibility of accidental blockage of some (fig. 5). Regular checking and cleaning of the vents is also required, to guard against the accumulation of dust and fluff (Seymour and Gibbons, 1982).

Finally, since a high disposal flow produces an intrusive hissing noise in some receiving systems (Houghton and Taylor, 1983), prospective purchasers would be well advised to audition any systems under consideration.

DISPOSAL SYSTEM

The disposal system may include disposal tubing connecting the receiving system to the fixed part of the disposal system. The draft BS requires that the inlet connector or connectors to the disposal system shall be other than 15-mm, 22-mm, 19-mm and 30-mm conical fittings. It further stipulates that, for an active system (see below), failure of the power source should not jeopardize the health of the patient, and an indicator should be provided to show the presence of flow in the system. The document also draws attention to the need to site the point of dispersal from the disposal system so as to minimize the entry of the waste gases into any building.

Disposal systems can be classified as *passive* or *active*. In a passive system, the work to drive the waste gases from the system is provided by the patient's breathing effort, whereas, in an active system, the waste gases are sucked out by a flow-inducing device such as a fan, a pump or an ejector. Thus, with an active system any leaks will be inward, whereas with a passive system they will be outward, and will increase pollution.

Passive Systems

These are attractive because of their simplicity and low running costs.

Piping direct to atmosphere

With this arrangement, the exhaust gases pass along a pipe through an outside wall and are then discharged to the atmosphere. In order to minimize the resistance presented to the patient, the tubing and piping used should be wide and as short as possible. This type of system is therefore not suitable for theatres remote from an outside wall. Guidance on the resistance of different diameters of piping, of bends, and of the pipe termination is given in the DHSS circular on operating department pollution (Department of Health and Social Security, 1976). This circular also points out the need to take due account of possible pressure changes in the system arising from wind effects on the termination. Strong winds can generate positive pressures exceeding 100 Pa on the windward face of a building, with negative pressures of a similar magnitude on the leeward face (Department of Health and Social Security, 1976); these pressures will be transmitted to the scavenging system if the disposal system is terminated against the wall (Ashbury and Hancox, 1977). The alternative is roof-top termination, which might reduce the positive pressure effects, but at the expense of increased suction effects (Department of Health and Social Security, 1976). Therefore, whatever type of termination is used, it is advisable that a closed receiving system incorporating negative pressure relief as well as positive pressure relief should be fitted. The DHSS document recommends that the discharge end of the pipe should be turned down to minimize entry of rain and dirt, and a tee with a downward 90° bend at each end should be fitted for roof-top termination; the open ends of the termination should be fitted with a wire mesh balloon to guard against insects.

Piping into extract air duct

If a theatre is remote from an outside wall, but has a convenient extract grille for the ventilation system, a passive disposal system can be fitted so that it discharges the waste gas through the grille into the exhaust duct (Bruce, 1973; Bethune and Collis, 1974; Whitcher et al., 1975; Hawkins, 1984). This method is suitable only for use with non-recirculating ventilation systems. One advantage of the method is that wind effects are avoided because the exhaust duct presents a constant pressure to the disposal system. The negative pressure at the exhaust grille is usually extremely small (Bethune, 1980), and its effect on the scavenging system is then negligible; thus the extract system does not suck the waste gases from the disposal system, but rather accepts the gases discharged by the disposal system, which are then entrained in the large ventilation flow. However, the suction pressure at the exhaust grille may, in some circumstances, approach 50 Pa (Whitcher et al., 1975; Bethune, 1980) and therefore it is again advisable to use a closed receiving system incorporating negative pressure relief. Under such conditions, the system ceases to be passive, and becomes a fan-powered active disposal system (see below).

As with through-the-wall systems, it is necessary to avoid long runs of piping to the discharge point, and so the viability of the method depends upon the availability of an exhaust grille close to the anaesthetic machine. Current concepts in operating suite design involve having a pattern of ventilating air flow determined by a "hierarchy of cleanliness", and with such a scheme the operating theatre is not fitted with an extract point, although the anaesthetic room and preparation room are (Ministry of Health, 1967; Department of Health and Social Security, 1983). Thus, in most modern hospitals, this form of scavenging requires the installation of considerable lengths of fixed pipework. It may be possible to circumvent this difficulty by connecting directly into the extract duct, if this passes conveniently close to the anaesthetic machine (Oulton, 1977). However, the negative pressure at the junction will be greater than at the exhaust grille, and this type of arrangement is probably better considered as a fan-powered active system (q.v.).

Active Systems

Active systems can use either the central piped vacuum system or a dedicated air mover, which can be a fan, a pump or an ejector.

Central piped vacuum system

Many reports have described scavenging systems that use the hospital vacuum system to provide the disposal flow (Schnelle and Nelson, 1969; Best, 1971; Davenport et al., 1976; Enderby, Booth and Churchill-Davidson, 1978). This practice has been criticized on several grounds (Department of Health and Social Security, 1976; Dorsch and Dorsch, 1984):

(1) Anaesthetic gases can degrade vacuum pump oil (McInnes and Goldwater, 1972).

(2) Certain anaesthetic gases are flammable, but the piped medical vacuum system is not designed for flammable gases.

(3) The vacuum system has insufficient outlets or capacity to provide scavenging disposal flows.

(4) The discharge point of the vacuum system may be unsuitable for the emission of anaesthetic gases.

The first two points now seem to be invalid, since subsequent investigations have failed to reveal any detrimental effect on vacuum pump oil and a simple calculation indicates that flammable agents will be diluted well below the lower limit of flammability before they reach the vacuum pump (Enderby, Booth and Churchill-Davidson, 1978; Wright, 1978). The third point would seem to have some validity, since many operating theatres have only two suction outlets and current DHSS recommendations specify a design flow of 80 litre min^{-1} for each theatre (Department of Health and Social Security, 1978). The vacuum system would therefore be unable to provide the magnitudes of disposal flow specified in the draft BS (100–130 litre min^{-1} for each receiving system). The fourth criticism will also be valid for many hospitals.

Fan-powered systems

Fans can not operate against large negative pressures and therefore it is necessary that the tubing and fixed piping in fan-powered systems (Whitcher et al., 1975; Hatch, Miles and Wagstaff, 1980) should be of large diameter, and kept as short as possible, in order to minimize resistance. Thus, the use of a single fan to serve a group of theatres usually requires the installation of a system of wide ducts. Such a system would be more inconvenient and expensive than a pump-driven system. However, it is sometimes possible to use the theatre extract system to provide both power and ducting, if the connection to the extract duct is made at a point sufficiently close to the extract fan (North West Thames Regional Health Authority, 1977).

Pump-powered systems

Pumps (Parbrook and Monk, 1975; Houldsworth, O'Sullivan and Smith, 1983b) can operate against large negative pressures and can therefore be used with considerable lengths of relatively narrow fixed piping. Thus, this type of system offers a convenient and economical method of providing disposal flows for a group of theatres from a single air mover. Furthermore, narrow disposal tubing, such as 13-mm plastic hose, can be used. This tubing is convenient to use, since it has the same handling characteristics as the gas supply hoses to the anaesthetic machine. If the inlet to the disposal system is positioned near the medical gas outlets, the disposal tubing can be run alongside the gas supply hoses and connected to the inlet with a quick-release probe.

Ejector-powered systems

These use compressed air or oxygen to entrain the waste gases by the Venturi effect (Jørgensen, 1974; Lai, 1977) or the Coanda effect (Asbury and Hancox, 1977). They have no moving parts and therefore require less maintenance than fan- or pump-powered systems. However, installation costs are generally greater than for pump-powered systems, since relatively wide disposal tubing and piping are required. Running costs may also be higher, especially if oxygen is used as the driving gas and high disposal flows are required.

Choice of Disposal System

The most appropriate choice of disposal system depends on the particular circumstances of the areas to be scavenged. In some older hospitals, a simple direct-to-atmosphere passive system may suffice, although due allowance must be made for possible wind effects. Armstrong and colleagues (1977) found that passive systems performed as well as active systems when they were compared in the same theatre. If the operating theatre is remote from an outside wall, it may be possible to use a passive system piped to the extract duct, although in some cases the need to install long runs of piping will make this an unattractive proposition. Thus, in many modern hospitals it will be necessary to install an active system. The use of the central piped vacuum system is probably best avoided, unless the last two of the objections discussed above can be shown to be inapplicable. Of the other active systems, the pump-powered type has some advantages, and most scavenging systems currently being installed in the U.K. have a disposal system of this type.

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WARNING DEVICES

J. H. KERR

Doctors and nurses are becoming increasingly reliant upon machines to assist in diagnosis and treatment and this tendency is particularly noticeable within the operating theatre and in intensive care areas. As old machines are replaced by more sophisticated and "safer" models and new ones are added to those already established, the number of alarm signals generated by their warning devices has multiplied rapidly and seems likely to increase further (Jenkins, 1984). At present it is not difficult, in a multi-bed intensive care area, to be able to count more than 30 auditory signals, each of which is accompanied by one, and often several, visual signals.

This proliferation of alarm signals, particularly of the auditory variety, is causing problems (Stafford, 1982; Kerr and Hayes, 1983). In a recent study on breathing system disconnections (Cooper and Couvillon, 1983), bedside staff stated that "multiple alarms sound, and the user does not know what has happened" and "many ventilator alarms sound like other alarms in the unit", while a physician, in discussing a fatality, reported that "the ventilator alarm was confused with the alarm from the EKG leads..." . It is clearly no longer sufficient to consider each warning device in isolation. A rational framework is required within which alarm signals can be deployed to provide the most effective protection for the patient's vital functions.

A warning device is a mechanism which generates a signal to inform the patient's attendant that a measured variable has moved from an acceptable to an unacceptable value. It is clear from this definition that the warning device must be considered as a component of a system composed of the patient (which, for purposes of this discussion, includes any machines which may be supporting vital physiological functions), measuring apparatus, warning device and attendant (fig. 1). All elements in this system can influence one another and the various interactions will be considered in turn.

A. EFFECT OF PATIENT ON MEASURING EQUIPMENT

A change in the variable being measured should induce a change within the measuring equipment.

B. EFFECT OF MEASURING EQUIPMENT ON PATIENT

Some of these effects are deliberate (e.g. skin heating with transcutaneous electrodes) and some accidental (e.g. impairment of mobility caused by leads); some are transient (e.g. arterial occlusion after catheterization) and some permanent (e.g. electrocution).

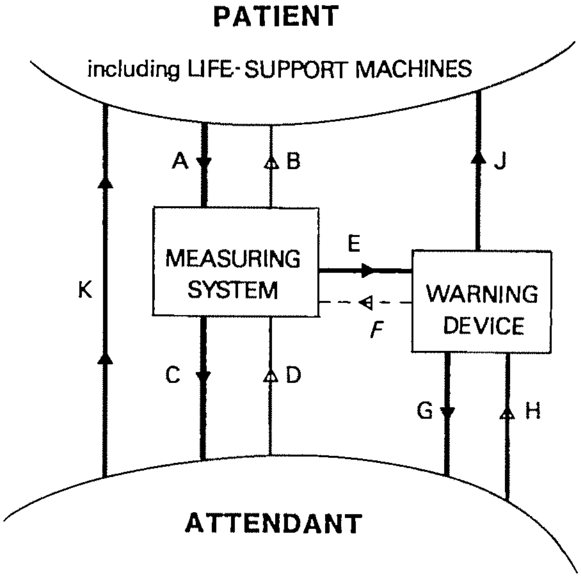

FIG. 1. Schematic diagram illustrating the inter-relationships between the patient, a measuring system with warning device, and the attendant. The letters A to K refer to sections within the text of the paper.

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C. EFFECT OF MEASURING EQUIPMENT ON ATTENDANT

Changes within the measuring equipment should be transmitted to the attendant. Analogue or digital visual methods are used most commonly for this purpose but, to be effective, require that the attendant is looking at the equipment; thus, auditory signals are used in some instances. The information may be displayed continuously (e.g. oxygen pressure dials) or intermittently, and the signals may be sub-divided into two types on the basis of function. One, exemplified by the light-flash, beep or click which accompanies an ECG complex or breath, indicates that a normal physiological action has occurred. The sudden absence of such a signal may fulfill a useful alerting function (as does the change in note during inspiration when a pressure pre-set ventilator becomes disconnected). The second type of information signal indicates both normal function and a degree of risk to the patient or, more commonly, to the attendant. Green lights which indicate that the mains electrical supply is on are the simplest examples of these, and the light that is illuminated when a laser is active and the "buzz" that sounds when the diathermy is in action, are further examples.

Although warning devices would not be required in an ideal world, they are necessary, since the attendant's attention may not be directed towards the displays when a significant change occurs, because of either other demands or loss of concentration. In addition, as automatic recording methods become more widespread, there is a risk that attendants may observe the measuring equipment displays less closely than when they had to transcribe readings onto written records.

D. EFFECT OF ATTENDANT ON MEASURING EQUIPMENT

The attendant often needs to calibrate the measuring equipment against a reliable standard.

E. EFFECT OF MEASURING EQUIPMENT ON WARNING DEVICE

The warning device is always an addition to apparatus which is measuring a physical, chemical or physiological variable. Variables may be simple (e.g. pipeline pressure) or complex (e.g. product of heart rate and systolic pressure; change of shape of an ECG signal) and they may be measured either from the patient or from machines connected to him. In all instances, however, the warning device changes from an inactive to an active (alarm) state when the value of the variable moves beyond a pre-set limit.

In the medical field, the ultimate purpose of any measuring system is to prevent changes in a variable which previous experience or physiological knowledge suggests are likely to impair the viability of the tissue, organ or organism. For a warning device to have any clinical relevance, therefore, it must be possible to trace a sequence of events between the change in the measured variable which activates the warning device (alarm event) and a change which produces damage within the patient (damaging event). Pathways between the "alarm event" and the "damaging event" may involve few or many steps and it may be helpful to classify alarms into two types, immediate and anticipatory, on the basis of the length of pathway.

Immediate alarms

Short pathways always involve measurements of physiological variables and tend to inform the observer that a potentially damaging state has already been reached in the patient: such warnings may be classified as "immediate" alarms. An alarm attached to a device measuring the brain oxygen concentration (Anon, 1982) represents the ultimate immediate alarm but, if its response time is longer than the time required to cause damage, it may be indicating that damage has occurred.

Anticipatory alarms

Other measurements, such as those made within the machines which are being used to support life, may have a longer pathway involving several steps between alarm and damaging event and may be classified as "anticipatory" alarms, because they are activated before deleterious physiological changes occur. A widely used alarm of this type is that which indicates a decrease in pressure in the oxygen supply to an anaesthetic machine or ventilator (Epstein et al., 1962; Wilson, 1965). From a clinical viewpoint, the anticipatory alarm would seem to be the more useful.

Factors Affecting Choice of Alarm Limits

For any variable (L), the limits of "normal" or "safe" values (Ln) may be considered to be those within which the probability of a damaging event

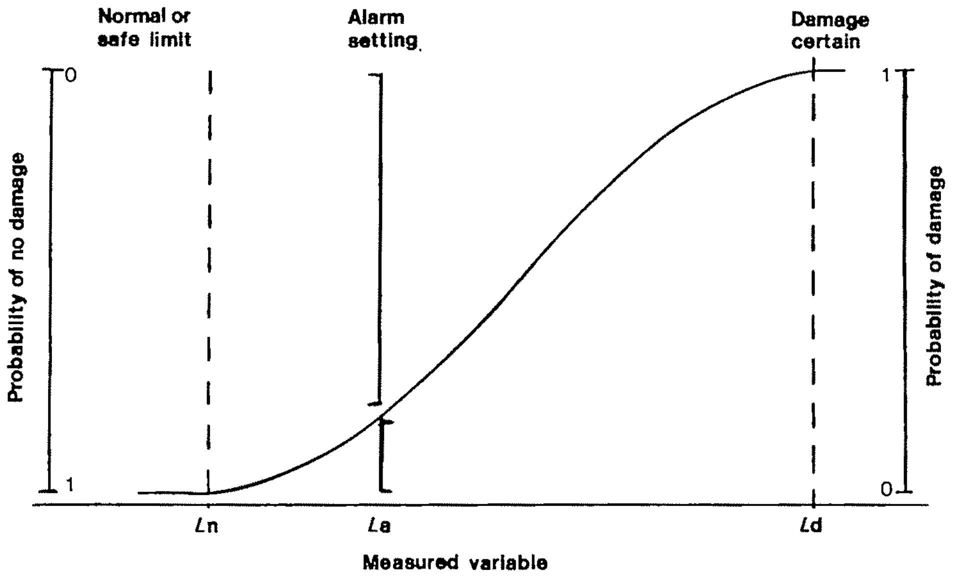

FIG. 2. Relationship between the value of a measured variable (L) and the probability that damage will, or will not, occur to the patient. The probability of damage increases as the value of L moves away from the "safe" limit Ln until it is certain when it reaches Ld. An alarm set at La to indicate that there is a small probability of damage is necessarily associated with a large probability that there will be no damage.

(Pd) is extremely small ($Pd \rightarrow 0$); in other words, the average time interval between damaging events is infinitely long. As the variable moves away from this "safe" range, the probability of a damaging event increases, and the average period between damaging events shortens, until a value (Ld) is reached at which damage becomes inevitable ($Pd \rightarrow 1$) within a short time (fig. 2). For any given variable, the relationship is unlikely to be the same for values above and below the normal range, so that each set of circumstances needs to be analysed separately.

The value of the variable at which the alarm is activated (La) lies between these two limits, and Pd at this point will have a value between 0 and 1 (fig. 2). It should be noted that, as the probability of damage increases, the probability of damage not occurring (Pnd) decreases in a complementary manner:

$$(Pd + Pnd = 1).$$

Effect of setting La *close to* Ld

The closer to Ld that La is set, the greater the possibility that a damaging event can occur without activation of the alarm. Such "false negative" responses are disastrous from the clinical viewpoint and undermine the attendant's confidence in the alarm as a predictor of damage. Other causes of "false negative" responses are listed in table I.

Effect of setting La *close to* Ln

If, on the other hand, La is set close to Ln, Pnd is large and it is more likely that the alarm will be activated unnecessarily (a type of "false positive" response). On most occasions, values of the variable may be expected to lie within or close to the "normal" range, so that the frequency with which the alarm is activated will also increase as

TABLE I. *Causes of incorrect responses by warning devices*

False negative responses
(1) Occurrence of damage before variable reaches alarm setting
(2) Failure of measuring system to register change in variable.
(3) Failure of warning device to respond to change in measuring system.

False positive responses
(1) No damage in spite of correctly activated alarm.
(2) Measuring system registers value exceeding alarm setting incorrectly.
(3) Activation of warning device before alarm setting reached.

the difference between *L*a and *L*n diminishes. The clinical instinct is to set *L*a close to, or even at, *L*n but user acceptance, and hence the overall effectiveness of the system, will be affected adversely if the inevitably false positive signal is generated frequently (Zwillich et al., 1974; Royston, 1982).

A system in which *P*d increases from 0 to 1 at a particular value of the variable ($Ln = Ld$) (e.g. one measuring a variation in the shape of an ECG waveform) has the advantage that there are no false positive or negative responses, but it will not predict damage, only signal it! The predictive value of the warning device will also be affected by the sensitivity of the measuring system and therefore its ability to detect changes between *L*a and the value of *L* at which the steeper increase in *P*d occurs. In an insensitive system, *L*a may have to be set within the normal range so that the alarm will be activated more frequently than would be the case if a more discriminatory system were used to measure *L*.

Time and probability of damage

Matters are complicated further by the realization that the probability of damage is related also to the period of time that the variable remains outside its normal or "safe" range. In general, the longer that a variable stays outside its "safe" limits, the greater the probability of damage and, since no living creature is immortal, it could be argued that a "safe" limit does not exist. It is possible, therefore, to envisage a set of iso-temporal lines representing the relationship between *P*d and *L*a–*L*n where the time involved is the period that the variable remains at *L*a.

If the rate of change of the variable is rapid, the time before damage occurs is likely to be shortened because *L* will quickly reach values at which *P*d is increasing steeply. Most monitoring devices, however, are not able to measure rates of change, although a crude indication may be obtained if the time interval between the signals produced by two warning devices set at different values of *L* is noted.

Delay between deterioration and alarm

An alarm is triggered only when the measurement has been outside the set limits for a period which will be determined by the response time of the measurement system (*T*m) plus that of the warning device (*T*w). (This period may be extended deliberately in certain circumstances, such as the delay built into some disconnection alarms based on airway pressure measurements so that the alarm should not be activated each time the patient's tracheobronchial tree is aspirated (Lamont and Fairley, 1965; Fodor et al., 1977).)

Delay between alarm and correction

Once the alarm has been activated, there will be a further period before corrective action restores the variable to its normal range. In some instances, this "correction time" (*T*c) is of the order of a few seconds (e.g. turning on a cylinder to restore the oxygen supply, or re-connecting a ventilator), but in others many minutes or even hours may be required (e.g. administering fluids to increase arterial pressure or digitalis to slow the heart rate). Particularly where *T*c is long, the probability of damage may be considerably underestimated if it is taken at the time when the warning device is activated. On the other hand, the estimation of probability of damage becomes more difficult as time lengthens.

Specificity of alarm message

Part of the difficulty in correcting an alarming variable may be that there are many possible reasons for the deleterious change. This situation applies particularly to physiological variables close to damaging events (e.g. brain Po_2) and a warning device on this type of variable may present the attendant with a wide range of possible corrective actions of varying effectiveness. *T*c is likely to be long and difficult to predict unless supplementary information is available to guide the attendant in the most appropriate direction. One reason for devising "intelligent" systems which are able to utilize data from a number of measuring systems is to provide such guidance and thereby reduce *T*c (Gravenstein, 1980). Other warning devices, notably those which are attached to variables with relatively long alarm–damage pathways, often present the attendant with a clear-cut corrective action so that *T*c can be predicted to within narrow limits.

Therefore, in choosing the alarm limit with a particular probability of damage in mind, the iso-temporal line used must be one such that $T > Tm + Tw + Tc$. The clinical value of a warning device that does not meet this condition will be minimal. Wherever the alarm limits are set, it must be accepted that the smaller the possibility of damage, the more likely it is that the alarm will signal a no-risk condition. Since these "false alarms" are inevitable (Smith and Beneken, 1980), the design and construction of the measuring system and warning device should minimize the number of incorrect responses for other reasons (table I).

It is possible that the techniques of signal detection theory (Moore, 1982), although developed for people rather than machines, might prove helpful in evaluating the relative effectiveness of different alarms.

F. EFFECT OF WARNING DEVICE ON MEASURING EQUIPMENT

(See "Effect of warning device on patient.")

G. EFFECT OF WARNING DEVICE ON ATTENDANT

Since the warning device has been added to the system because of the fallibility of the attendant, the relationship between these two elements is crucial. Theoretically, warning devices can be devised to transfer information to the attendant through any of his senses, but in practice the visual and auditory routes are used most commonly.

Ideally, a signal produced by a warning device should not only indicate to the attendant that something is wrong, but also give him some idea of what needs to be done and how quickly (Hyman, 1982). To achieve this, it must be clear which patient is involved and then which measuring system is unsatisfactory. While a visual alarm located upon a particular item of equipment should be unequivocal, it (like the variable display) is effective only if the attendant happens to be looking at it. Auditory alarms are used, therefore, to draw the attendant's attention to the problem area within which more specific information about the difficulty is presented in visual form.

Priority

The concept whereby different signals are used to indicate conditions which are thought to justify responses of varying urgency seems to be widely accepted. Warning signals indicating three levels of urgency (Emergency, Cautionary and Alerting conditions) have been proposed (table II), although there is less agreement about exactly what separates one category of conditions from another. Logically, it would seem that a worst-case analysis of the time between the alarm and the damaging events could provide a basis for differentiating degrees of priority, although this might exclude the effects of the correction time. The computer simulation of the respiration process, MACPUFF (Dickinson, 1977), has been used to determine the delay between various respiratory catastrophes and a "fatal" decrease in brain $P\mathrm{o}_2$ (table III), showing that continued ventilation with an anoxic gas mixture could "kill" in less than 2 min, whereas disconnection takes more than twice as long.

Visual Warning Signals

Where coloured lights are used, there is a well established convention which allocates red and yellow to alarm states and green to a normal operating condition (IEC, 1977). Common sense would indicate that the light should be placed in a prominent position upon the equipment, and it

TABLE II. *Priority classification of warning signals*

Condition	Signal	Warnings Visual	 Auditory	Response
Emergency	W A	Flashing red	Fast (E)	Immediate action
Cautionary	R N	Flashing yellow	Slow (C)	Prompt action
Alerting	I N G	Continuous. Not red or green. Yellow preferred.	None unless specified by another standard (not E or C)	Increased vigilance
Information (see section C)	Information	Not red or yellow. If green = equipment ready for use.	Prefer none. NOT E or C	Confidence

TABLE III. *Simulation of respiratory catastrophes on MACPUFF. Initial lung values and blood-gas tensions were noted immediately before inducing a change in the model together with the time to "death"* ($P\text{brain}_{O_2}$ *to zero) or to a fresh steady state. The changes investigated were (a) Minute volume to zero (disconnection), (b)* $F_{I_{O_2}}$ *to zero (oxygen supply failure) and (c)* $F_{I_{O_2}}$ *reduced from 50 to 21% (substitution of oxygen with air) at a range of lung volumes and venous admixtures*

Initial values							Effect	
FRC (ml)	$\dot{Q}va/\dot{Q}t$ (%)	Min. vol. (litre min^{-1})	$F_{I_{O_2}}$ (%)	Pa_{O_2} (kPa)	$P\text{brain}_{O_2}$ (kPa)	Change	$P\text{brain}_{O_2}$ (kPa)	Time (min)
3000	8	8	21	10.1	3.6	Min. vol. → 0	0	6.5
1250	8	8	21	10.0	3.2		0	3.0
3000	8	8	50	26.7	3.4		0	10.3
1250	8	8	50	27.6	3.5		0	6.0
3000	20	8	50	12.5	3.3		0	10.3
3000	31	9.6	50	8.8	3.1		0	8.5
1500	31	9.6	50	8.8	3.2		0	5.0
1250	20	8	50	12.7	3.6		0	6.0
3000	8	8	21	10.0	3.5	$F_{I_{O_2}} \to 0$	0	4.5
1250	8	8	21	10.0	3.6		0	2.5
3000	20	8	50	12.5	3.3		0	2.25
3000	31	9.6	50	8.9	3.1		0	2.25
1500	31	9.6	50	8.8	3.1		0	2.0
1500	39	9.6	50	7.7	3.8		0	1.75
1250	20	8	50	12.7	3.6		0	1.75
1500	31	9.6	50	8.9	3.1	$F_{I_{O_2}} \to 21$	4.4	15
1500	39	9.6	50	7.7	3.9		4.0	15
1250	20	8	50	12.6	2.9		2.4	15

has also been stressed that it be visible through a wide arc. Visibility may be improved further by making the light flash or rotate and by placing it near a reflective surface.

At present, there is no convention applying to alpha-numeric indicators or to VDUs and it is perhaps time that one was agreed for these types of display. They have the potential of being able to transmit more detailed information than simple lights, with the disadvantage that the attendant will have to take the time to assimilate the message before being able to act upon it. The use of such displays in preference to a light should be dictated by the complexity of the response expected from the attendant: a situation requiring a simple response (e.g. reconnecting the ventilator) may be signalled by a simple light code, whereas one requiring a more complex analysis using additional information may be transmitted more effectively using some type of alpha-numeric display (Beneken et al., 1983).

Auditory Warning Signals

Auditory alarms are particularly useful because they can draw an attendant's attention towards a problem even when it is not in direct view, but there is a danger that this mode of communication may be overloaded unless reserved for carefully selected signals (Hyman, 1982; Cooper and Couvillon, 1983; Kerr and Hayes, 1983). In general, audible signals should be used only to warn that damage to the patient is likely to occur *within minutes* unless action is taken.

Most of the auditory warnings currently produced by medical equipment are continuous or rapidly intermittent tones of constant (and usually high) pitch. Their loudness (sometimes in excess of 75 dB) is often uncontrollable and designed to attract the attendant's attention across a moderately noisy room. Such sounds tend to startle the attendant (and the patient), so that the initial reaction is to switch off the noise rather than to treat the patient. Besides inhibiting logical thought while in action, high-pitched sounds are difficult to localize; this problem will be familiar to all who have worked in a multi-bed ITU in which several infusion pumps have been in use!

Current warning sounds are limited by the inexpensive but robust vibrators which are utilized. With the increasing availability, decreasing cost and vastly greater flexibility of electronic and microprocessor systems (Peters, 1980), it is an opportune time to re-think the characteristics of alarm sounds on medical equipment.

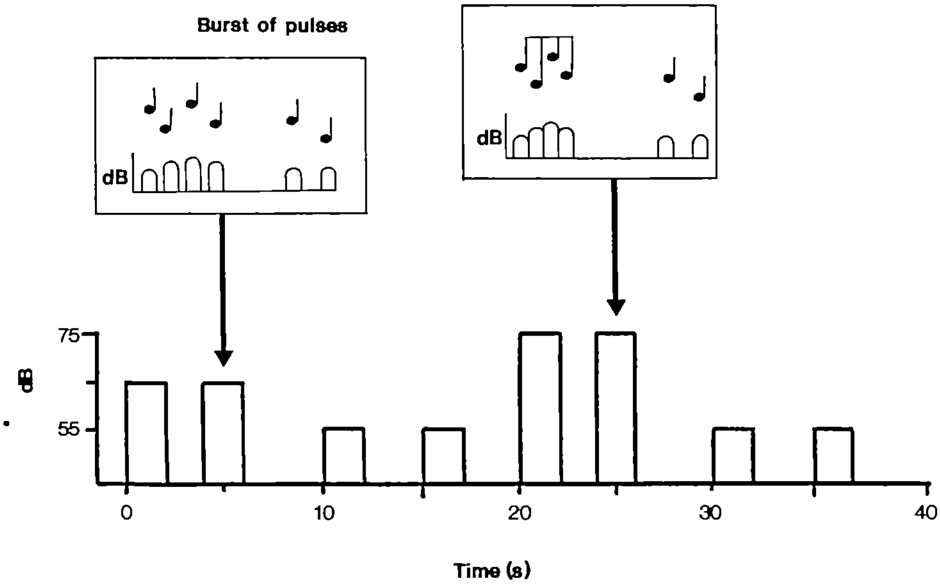

FIG. 3. Diagram to illustrate the general structure of the proposed new emergency alarm sounds. The "bursts of pulses" depicted in the boxes on the upper part of the diagram are composed of pulses of sound (notes chosen at random to indicate pitch changes) with varying amplitudes and time intervals. Each alarm sound will have its own characteristic pulse, sequence of pitch changes and temporal pattern, somewhat analogous to the "calls" of different birds. Each of the blocks on the time axis below represents a repetition of the burst of pulses (call). The initial two bursts are played at intermediate loudness and are then repeated at a lower amplitude. In addition to the automatic attenuation of the loudness, there are significant silent intervals between repetitions to encourage the attendant to treat the patient before feeling impelled to silence the alarm signal. If the alarm condition continues for longer than about 20 s, the next two bursts are played both more loudly and more quickly. The quicker repetition of the burst illustrated on the right is reserved for use in emergency alarm signals.

New Warning Sounds

Based on work carried out to re-design auditory warnings for aircraft flight-decks (Patterson, 1982), it has been proposed that "new" medical alarm sounds should consist of a sequence of notes in a distinctive rhythm, somewhat analagous to a bird call (fig. 3). The notes will be "rounded" to minimize their startling effect and each will be composed of at least four harmonics, to assist in localization. The sounds will not play continuously, but there will be quiet intervals lasting several seconds between repetitions of the "call", to reduce the tendency to silence the alarm before dealing with the problem. Urgency will be indicated by playing the call more quickly rather than more loudly, although the loudness of some of the later repetitions may be increased in case the attendant has moved out of earshot.

Alarm sounds will be differentiated from one another at three levels: (a) because of their harmonic structure, the notes used in each alarm will resemble those produced by a different musical instrument; (b) the pattern of loudness and of pitch of the successive notes will vary from one alarm sound to another, as will (c) the time intervals between the notes, producing a rhythm which should be distinctive even to the tone-deaf.

Allocation of Alarm Sounds

Having designed more acceptable warning sounds, the next stage in the process of rationalization is to agree how they should be deployed. Three over-riding considerations must be fulfilled.

(1) Each alarm sound must have the same meaning wherever encountered within the hospital. This principle has already been adopted in society at large, where the sounds produced by telephones, fire bells and emergency vehicles are characteristic, internationally similar and therefore immediately recognizable.

At present, the auditory signals provided on medical equipment are chosen by the manufacturer and may both resemble those with entirely different significance and differ from those with a similar meaning. In practice, staff have to learn the significance of a fresh set of sounds each time they move to a new environment and confusion can be caused when new equipment is added to the existing stock. Once a set of alarm sounds has been learnt, however, nursing staff do find the differences between the sounds produced by different items of equipment valuable, and so arrive at the bedside with some idea of the likely problem.

(2) The number of different alarm sounds must be limited to an absolute maximum of 10 and preferably not more than six should be deployed in any particular environment. Recent research on hearing indicates that, even under unstressed circumstances, humans do not easily learn and remember the significance of more than about eight arbitrary sounds (Patterson, 1982).

(3) The allocation system must be able to accommodate future technological developments.

Within these constraints, there are several possible ways in which alarm sounds could be allocated, and some will be considered further.

A single all-purpose alarm sound

In this approach, all medical equipment would produce the same alarm sound, although it would be possible to distinguish two levels of urgency by playing the sound at two speeds. The main advantage claimed for this simplistic approach is cheapness and ease of manufacture, but it totally ignores one of the problems repeatedly cited by ICU staff in the FDA Report on breathing system disconnections (Cooper and Couvillon, 1983), which was that "all alarms sound the same". This solution represents a complete departure from current practice whereby staff learn and use the slight differences between sounds, and it seems certain that confusion at the ITU bedside, where five or six items of equipment would all produce the same alarm sound, will be increased. The single alarm sound might be appropriate for a common warning generated by a "bus" system in which alarm signals from a variety of equipment items are routed together (see discussion on centralized alarm systems).

A "priority-based" approach

There would be three different alarm sounds, each indicating a particular level of urgency. The highest level (emergency) could be limited to measurements which indicate the possibility of tissue damage within, say, 3 min; the next level (caution) would be given a time limit of 6 min or so. The third level would be used for important, but less time-limited situations. A possible distribution for sounds on this basis is shown in table IV.

An "equipment-based" approach

Particular types of equipment would be allocated specific alarm sounds. It would mean that each item of equipment produced only one alarm sound whatever variables were being measured (e.g. the sound produced by a ventilator with an integral oxygen analyser could have a different significance and require a different response from the attendant from that produced by a ventilator without integral analyser).

A further problem with this approach is that, even now, it would be difficult to limit the number of sounds to the six or seven that can be learnt and remembered easily, and that new types of equipment would require further sounds.

A "risk-based" approach

Damage to living tissues can be caused by relatively few agencies. Potentially damaging interfence with metabolic activity can occur with changes in (1) oxygen availability, (2) acid–base status, (3) temperature, (4) lack or excess of drugs, (5) the structural integrity of the tissue and (6) radiation.

If each risk were allocated its own alarm sound, the same signal would be produced by all measurements, which could ultimately lead to hypoxia ranging from a brain oxygen monitor, through IPPV disconnection detectors, to circulatory monitors and leak detectors in heart–lung or dialysis machines. On the other hand, a ventilator would need different alarm sounds for oxygen delivery failure (1), low minute volume (2), humidifier malfunction (3) and high airway pressure (5).

A "risk and response-based" approach

This approach is a combination of the previous two. Six alarm sounds have been allocated on the bases of patient risk and of the corrective action required from the attendant. Each sound will have a fast (emergency) and a slow (cautionary) version.

Hypoxia (*H*): failure to deliver oxygen: this alarm sound will focus the attendant's attention onto the oxygen supply pathway leading to the sensor site.

Ventilatory problems (*V*): interference with

TABLE IV. *Allocation of alarm sounds (a) by priority, and (b) by risk and action. In the risk part of the table, the type of sound (see text) is indicated by a capital letter (H = hypoxia; V = ventilation problem; C = cardiovascular problem; P = artificial perfusion device problem; D = drug administration problem; T = thermal risk), and the form by a small letter (e = emergency; c = caution). Notes: (1) If a thermal cut-out is used so that further heat transfer is prevented (proposed in the Draft standard for humidifiers), a CAUTION alarm is sufficient. (2) These devices will have to be capable of producing both EMERGENCY and CAUTION sounds. The user will set the desired level depending on the potency of the drug delivered. (3) No audible alarm sound needed*

	(a) Priority level		(b) Risk
Measured variable	Emergency sound	Caution sound	Type of sound
Brain oxygen (low)	+		H e
Intravascular oxygen (low)	+		H e
(high)		+	H c
Trans cutaneous oxygen (low)	+		H e
(high)		+	H c
Gaseous oxygen (low)	+		H e
(high)		+	H c
Oxygen supply (if air NOT substituted)	+		H e
Oxygen supply (if air substituted)		+	H c
Minute volume (low)	+		V e
(high)		+	V c
Airway pressure (low)	+		V e
(high)	+		V e
Apnoea indicator	+		V e
End-tidal carbon dioxide		+	V c
Cardiovascular monitors	+		C e
Balloon assist devices	+		C e
Haemodialysis			
Air	+		P e
Disconnection	+		P e
Low flow		+	P c
Ultra-filtration rate		+	P e
Fluid temperature (high) (1)	+ ?	+ ?	T ?c
Plasmapheresis			
Air	+		P e
Disconnection	+		P e
Low flow		+	P c
Fluid temperature (high) (1)	+ ?	+ ?	T ?c
Syringe pumps (2)	+ and	+	D e & c
Infusion pumps (2)	+ and	+	D e & c
Infusion controllers (2)	+ and	+	D e & c
Inhalation anaesthetic meters	+		D e
Enteral feeding pumps (3)			
Incubator temperature (high) (1)		+	T c
(low)		+ ?	[T ?]
Radiant heater temp. (high) (1)		+	T c
(low)		+ ?	[T ?]
Humidifier temp. (high) (1)		+	T c
Heating blankets (high) (1)		+	T c
Brain activity (EEG)	+		H e

ventilation, including both disconnection and high airway pressure (barotrauma risk)—the attendant needs to check the airway and ventilator.

Cardiovascular problems (C): the attendant's attention is drawn to the patient's circulatory status. These sensors will probably be of the immediate type.

Interruption to artificial perfusion (P): problem with an artificial circulation which may precede (C)—the attendant must look first at the perfusion device (e.g. haemodialysis machine). A good example of the anticipatory alarm.

Drug administration error (D): this alarm sound will indicate that an infusion pump or powered syringe being used to infuse a drug needs attention. Because these devices can be used to give agents which will justify either an emergency alarm (e.g. inotropes, sodium nitroprusside), or a cautionary auditory warning (e.g. analgesics, hypnotics) or only a visual alarm signal (e.g. parenteral nutrition), a method whereby the user can choose the appropriate level will have to be provided.

Thermal risk (*T*): heating and cooling devices capable of producing damaging local or general temperature changes.

A distribution of these sounds is shown in table IV.

The strength of this solution is that it maximizes the transmission of information by the auditory route and capitalizes on the capability to learn and recognize six alarm sounds. It represents a rationalization of the present situation in which staff learn and use different but inconsistent sounds.

This approach, however, will make it necessary for some machines to produce more than one sound (e.g. a ventilator with integral oxygen analyser and heated humidifier would produce three sounds, namely H-ypoxia, V-entilatory and T-hermal, although each would indicate to the nurse that a different response was required). The use of microprocessor technology, likely for other reasons, will minimize this problem because only software modifications will be required. Since this solution is based ultimately upon patient risk, it should accommodate future technological developments.

It must be stressed, however, that there is, at present, insufficient evidence to provide overwhelming support for any particular allocation system, so that it will be necessary to carry out research to provide the information from which the optimal solution can be chosen.

H. EFFECT OF ATTENDANT ON WARNING DEVICE

Testing the alarm

The attendant's first requirement is to be able to test the warning device to assure her/himself that it will produce the expected signal if appropriate. Alarm testing systems are of two types: one passes power through the output device which produces the warning signal and thus proves only that power is available and that the light or noise, or both, is produced. The other tests the complete system by permitting the variable being measured to be manipulated beyond the alarm limits. Many warning devices are activated automatically when the measuring system is switched on, but if the equipment is not to be connected immediately, either because the patient has not arrived or because the warm-up time is prolonged (e.g. humidifier hot-water baths), some means of attenuating the auditory alarms will be needed.

Disabling the alarm

Alarm on/off switches are potentially lethal because the warning device may be left disabled and thus cause an over-reliant attendant to fail to observe a dangerous condition (Hyman, 1982). A second danger in providing an on/off switch is that, during use, the attendant may disable the warning device deliberately if she/he becomes irritated by it or discovers that it does not help with clinical management, or both (Zwillich et al., 1975; Fodor et al., 1977; Mills, 1980). It has been stated that "the ease of disabling ventilator alarms either deliberately or inadvertently is overall the most important contributory factor in injuries" (Cooper and Couvillon, 1983). Manufacturers of medical equipment often make this action more likely by providing aggressively intrusive signals in attempting to ensure that their equipment can never be faulted because it failed to notify the attendant of deterioration (Hyman and Drinker, 1983). This trend carries the risk that more and more of these abrasive warning devices clustered around the bed may be deactivated, with the result that the patient may lose the undoubted benefits of some of the anticipatory alarms.

It should not be necessary to disable visual alarm signals under any circumstances and, if a case can be argued for providing a means of silencing an auditory signal, the same arguments will refute the need for any auditory warning signal. Attempts have been made to produce warning devices without on/off switches (Ward, 1968; Fodor et al., 1977), and other compromises introduced by alarm system designers have included limiting either the duration of time for which an auditory alarm can be silenced or, in the case of some warning devices with variable settings, by incorporating safe limits into the machine (e.g. the 20% minimum value on in-line oxygen monitors). These requirements, however, increase the complexity of warning devices and may impair their reliability and ease of use (Hyman, 1982).

Centralized alarm systems

A broader approach to these problems is to route all the warning signals onto a common alarm system which would display an indication of the piece of equipment involved as a light on an "alarm board" or a message on a VDU. One sound could be used to draw the attendant's attention to the message centre and, in all but a very few large ITUs, it would be possible for a specific alarm sound to be allocated to each bed-space. Such a system would lend itself to the incorporation of "intelligence" if a microprocessor was included to analyse the pattern of behaviour of more than just the alarming variable (e.g. the "smart" ventilator alarm, which analyses the pressure waveform in addition to the actual pressure (McEwan and Jenkins, 1983), or a cardiovascular monitor the ECG alarm of which is activated only if accompanied by a significant change in the arterial pressure waveform) (Gravenstein, 1980); but this development introduces the problems of software design and maintenance. Centralized alarm systems of this type are being installed in the aircraft cockpits of modern airliners to bring together the warnings from a variety of measuring systems installed by different manufacturers.

There are, however, significant practical differences between the relatively fixed layout of the anaesthetist's "cockpit" in the operating theatre (Gravenstein, 1980) and that in the ICU where there is much greater variability both in the layout (Kerr, Coates and Gale, 1985) and in the amount of equipment in use. If a centralized alarm system is to be used, it is necessary to provide a means for each measuring device to transmit its warning signal to the common system.

Wires. If wires are to be used, one from each item will have to be connected to the common "bus". It is possible that this connection may be forgotten, particularly if an item is brought in because of an emergency, in which case a means of indicating that the warning device is inactive will have to be provided (another auditory signal?). If the wires are connected, the already chaotic bedside environment will be made worse (Cesarano and Piergeorge, 1979).

Telemetry. Signals can be transmitted from the measuring equipment to the common alarm system using radio waves but, if this mode is to be used, a suitable transmitter will have to be incorporated in each item of equipment. This will be expensive, and interference from the other electrical equipment gathered around the patient may impair the reliability of the system.

Infra-red signals. Infra-red signals carrying the alarm messages can be generated using rather simpler and less expensive devices and might be directed up to a receiver area in the ceiling above the bed or operating table. Care would be necessary, however, to avoid blocking the signal by interposing physical bodies between transmitter and receiver.

This common bus approach to the problem presents significant technical and ergonomic difficulties and should, I believe, be considered as a somewhat futuristic ideal at present. For the moment, the approach discussed earlier, which builds upon methods that are already widely used, seems a more practical and flexible alternative.

J. EFFECT OF WARNING DEVICE ON PATIENT (INCLUDES LIFE SUPPORT EQUIPMENT)

In intensive care areas, the signals produced by some warning devices disturb and frighten patients, particularly if powerful lights are flashed in their eyes or if strident auditory signals are used. Patients are worried by being unable to distinguish between their own and others' alarms and by signals which remain uncorrected (Parker et al., 1984). It seems inappropriate, therefore, to use voice synthesizers to issue warnings in plain speech where conscious patients are involved, so "coded" signals will probably persist, at least on equipment used at the bedside.

Feedback

The warning device can be organized to modify the behaviour of a machine which is supporting physiological functions in a patient. Many oxygen failure alarms cut off the supply of other gases if activated and thus prevent the supply of an anoxic gas mixture (safety interlock) (Epstein et al., 1962), and some even switch the circuit so that air is inspired (see table III). Some mains-failure warning devices switch the power supply of the equipment to a battery or generator back-up on activation. Heating devices can, and should, be arranged so that the activation of the over-temperature alarm automatically disables the heating circuit. Such stratagems alter the significance of the alarm signal by actively reducing the risk of patient damage, and may therefore lessen the degree of priority of the signal.

K. EFFECT OF ATTENDANT ON PATIENT/ LIFE SUPPORT MACHINE

One of the most important objectives of the attendant's training program must be to enable her/him to recognize the significance of the signals produced by the different warning devices and thereafter to take the most appropriate corrective action (Hyman, 1982). With the more widespread availability of microprocessor based systems (Hyndman, 1980), it is possible to give specific commands both on VDUs and by speech synthesizers.

CONCLUSION

This essay shows the folly of trying to analyse what seems intuitively obvious. The attempt has been made because discussions are taking place within both the International Standards Organisation and the British Standards Institution, with the aim of rationalizing the alarm signals utilized within the hospital, and it seems essential that the true complexity of the topic be appreciated. If a soundly based Standard for alarms is to be produced, it must be recognized that research is necessary and that, even though it falls outside the usual physio–pharmacological framework, it does offer definite benefits in terms of patient safety. It will be necessary to collaborate with engineers and psychologists, both to generate techniques to evaluate the relative importance of the growing number of warning systems, and to allow experiments with new systems in clinical settings.

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NATIONAL AND INTERNATIONAL STANDARDS FOR ANAESTHETIC EQUIPMENT

R. GREENBAUM

According to the British Standards Institution (BSI), the purpose of standardization is to provide technical criteria, accepted by consensus, which promote consistent quality and economic production. Standards simplify manufacture and encourage interchangeability. In addition, they rationalize processes and methods of operation, making communication and the exchange of goods and services easier. Their use gives confidence to manufacturers and to users alike and promotes the quality of life, safety, health and the protection of the environment. It is also intended that their use will promote trade by removal of barriers caused by differences in national practices.

British Standards are classified into four main categories:

(a) Terminology and classifications.
(b) Methods of measuring, specifying and testing.
(c) Specifications for materials including dimensions, performance and safety.
(d) Codes of practice and guidelines.

BSI aims to achieve alignment with the International Standards Organization (ISO) wherever possible, both in technical content and in the presentation of documents. Sometimes, this leads to changes in long established British practices, although often British practice becomes accepted internationally. The cost of achieving international agreement is a delay in producing ISO standards compared with purely national standards.

Standards are prepared by committees composed of individuals representing interested parties. In anaesthetic and intensive care equipment committees, clinicians are nominated by professional associations including the Association of Anaesthetists, the Intensive Care Society, the British Paediatric Association and the British Association of Otolaryngologists. Manufacturers are represented by appropriate trade associations including the British Anaesthetic and Respiratory Equipment Manufacturers Association, Scientific Instrument Manufacturers Association, British Rubber Manufacturers Association, British Surgical Trades Association Incorporated, Medical Sterile Products Association, and Instrument Safety (Protective Equipment) Manufacturers Association. Finally, the Department of Health and Social Security is represented by its experts in each particular field.

Standards committees provide an important forum for the exchange of ideas between the profession, the manufacturers and the DHSS. Many ideas generated at their meetings are adopted and tried by manufacturers long before the final standard is published.

Medical Standards aim to promote safety. However, "safety" has many connotations, for example, withstanding sterilization, interchangeability of components, prevention of electrical hazards, prevention of "pollution" hazards. It must be appreciated that equipment standards cannot provide "safety" to an uneducated and untrained user. They do not replace training and familiarity with equipment.

Compliance with every requirement in a standard is assured by a corresponding test. The test must be feasible, cheap and generally capable of operation by the supplier, the purchaser and any third party testing agency. Tests may be demanded for each and every item of a product, representative samples or towards testing a general design and manufacturing process (Type Test). Markings and contents and manufacturers' information handbooks are also specified. Products complying with the standard are marked with the number and date of the standard and, where appropriate, with the manufacturer's name and trademark.

Many standards include endurance tests, but standards cannot prescribe the number of years

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of working life of a product as this would depend on use, maintenance, replacement of defective components and the nature of the product. Nevertheless, the ability of an item to perform its required function under stated conditions of use and under stated conditions of preventive and corrective maintenance is the province of standards, outlined in BS4778 "Glossary of Terms used in QA" and BS5760 "Guide to Reliability Programme Management".

Countries vary in the speed with which standards must be implemented and in the legal status given to standards. Normally, standards provide consumer confidence without the arbitrary nature of legislative measures.

Standards relating to anaesthetic and intensive care equipment are shown in the appendix. Committees cover such diverse subjects as blood transfusion and hypodermic equipment, medical gas cylinders, sphygmomanometers, etc. Standards relevant to anaesthesia have been reviewed by Hillard (1968), Dinnick (1978) and Thompson (1983). The particular topics which it is intended to discuss in this paper are those under the purview of ISO Technical Committee 121—anaesthetic and respiratory equipment and supplies, related devices and supply systems and the equivalent British Technical Committees SGC 44, 45 and 46.

MEDICAL GAS PIPELINES

The current draft International Standard describes requirements for the installation, commissioning and operation of pipeline systems. It is designed to ensure that there is no risk of failure of gas supply without adequate warning and that the plant is designed to prevent interchangeability between different gas services. Specifications include requirements for reserve supplies, warning systems, testing and commissioning procedures and pipeline identification. Annexes to the Standard provide recommendations for such events as extending a pipeline system and emergency procedures when the supply of gas fails in one or more clinical areas.

TERMINAL UNITS AND HOSE ASSEMBLIES
BS5682:1984

The safety of piped medical gas systems is dependent on the performance of every connection in the distribution system. In the British and International Standard Committees, particular attention has been paid to ensure that the connectors are gas-specific. In the U.K., non-interchangeable screw-threaded connectors (NIST) are specified, in North America an alternative diameter indexed safety system (DISS) is used (CGA, 1978). Pressure decrease–flow specifications are given and tests of hose kinking, hydrostatic bursting pressures and electrical conductivity are incorporated in BS5682:1984.

CYLINDERS AND CYLINDER CONNECTIONS
BS1319: 1976 AND ISO/R32,407

There is increasing application for the pin-indexed yoke connections described in ISO R32,407 and BS1319. Consideration is also being given to a standard for pressure regulators for medical gases. Cylinder gas colours in the U.K. comply with ISO R32,407 and BS1319C; however many countries have national standards of colour coding which are given precedence over those of the international standard.

CONTINUOUS FLOW/INHALATION ANAESTHETIC APPARATUS (ANAESTHETIC MACHINES)
ISO5358: 1980

ISO5358 (1980) specifies the basic performance requirements of the "Boyle's Machine" and its components. It is an important document because, although patient hazards caused by faulty anaesthetic machines are responsible for only a small minority of accidents, they are persistent, highly publicized and largely preventable. Some important provisions in this standard are therefore summarized. The sequence in which each component appears, follows the direction of gas flow.

Inlet connections

Pipeline inlet connections shall be the body of the DISS or NIST fitting. Cylinder connections must be non-interchangeable between different gas services, and "hanger yokes" must comply with the pin index safety system described in ISO407.

Pressure gauges and cylinder contents indicators

Gas supplied by pipeline from central supplies at reduced pressure may be monitored by pressure gauges which are capable of indicating a pressure of at least 33% greater than that of the nominal pipeline pressure. Gases supplied at cylinder pressures must be monitored by a cylinder pressure gauge or contents indicator which shall be capable of indicating a pressure of at least 33 % greater than the normal maximum working pressure of the cylinder at 20 ± 3 °C.

Such gauges are required to have a maximum error of $\pm 4\%$ of the full scale reading and all gauges of this type must have substantially equal span angles of not less than 180° and not more than 300°.

Pressure regulators

All gases supplied to the machine at pressures in excess of 100 kPa must be provided with automatic pressure regulators. The delivery pressure from the regulator to the flow control valve must not increase by more than 10 % of its initial value when the flow of gas is reduced to the lowest flow for which the flowmeter for that gas is calibrated, and must regulate pressure to within 0.7 kPa per 100 kPa change in supply pressure.

Flow control valves

Flow control valves must increase flow by being turned counter-clockwise, and *vice versa*. Under conditions of constant inlet and outlet pressure and at constant ambient temperature, these valves must maintain established flow to within $\pm 10\%$ or 10 ml min^{-1}, whichever is the greater.

At an inlet pressure of at least 300 kPa, the flow control valve knob must be rotated by at least 90° to achieve adjustment of the associated flowmeter through the upper 90° of its scale range.

Oxygen flow control knobs must have the unique characteristic profile which is described in the standard and may project beyond the other flow control knobs.

Flowmeters

Introduction of oxygen to a common gas manifold upstream of other gases has led to the delivery of hypoxic gas mixtures as a result of oxygen leakage through cracked flowmeter tubes, poor sealing of the flowmeter tube or other faults permitting such leakage (Eger, Hylton and Irwin, 1963; Bishop, Levick and Hodgson, 1967; Katz, 1968; Liew and Gandenran, 1973; Gupta and Varshneya, 1975).

The standard therefore demands that, where oxygen and other gases are delivered by their respective flowmeters into a common manifold, the oxygen must be delivered downstream of all other gases. This may be achieved either by having the oxygen flowmeter on the right extremity of the flowmeter bank, as in the U.S.A., or by having the oxygen flowmeter sited on the left, as is established in British practice, but making sure that the oxygen joins the other gases downstream.

Where mixing devices are used in addition to or instead of flowmeters, the percentage of oxygen and the total flow of the gas mixture delivered must be indicated.

It is to be hoped that there will be more detailed requirements for the accuracy of flowmeters when the standard is reviewed in 1985.

Vaporizers

Requirements are described for flowmeter-controlled vaporizer systems, electrically heated vaporizers and concentration-calibrated vaporizers.

To prevent cross contamination of the contents of one vaporizer with another agent, it is recommended that a system be provided which isolates vaporizers from each other and prevents gases passing through the vaporizing compartment of one vaporizer and then through that of another. Work is currently being undertaken on the standardization of fittings for detachable vaporizers.

Concentration-calibrated vaporizers must not permit liquid discharge through the vaporizer outlet even at flows up to 75 litre min^{-1} and must not vary their average delivered concentration by more than 20 % at 20 ± 1 °C and 1 standard atmosphere pressure when tested at a prescribed filling level, pressure fluctuations, gas flows and vaporizer settings.

The International Standard Committee has worked for many years on standardization of agent-specific filling systems for vaporizers and this project is still undergoing study. Unfortunately, some of these devices have been prone to air locks, leakage and, under certain conditions, permit over-filling of their vaporizer. However, the main problem is that it has not proved possible to have an international system for restriction of certain designs and sizes of bottle necks to use with anaesthetic agents. Nevertheless, certain countries have adopted national standards for these filling systems.

Common gas outlet

A common gas outlet must be provided with a 22-mm male conical fitting incorporating a co-axial 15-mm female connection. This fitting may additionally be a screw-threaded, weight-bearing fitting in accordance with ISO/DIS5356/2. The bending movement and torque that the common gas outlet must withstand are 3 Nm and 10 Nm for the two fittings, respectively.

Oxygen flush valves

Emergency oxygen flush valves may be provided to supply an unmetered oxygen flow at the common gas outlet, but their accidental use has led to pulmonary barotrauma and patient awareness. The standard thus requires any flush valve to be self-closing (if specifically requested by a user, an over-riding mechanism can be provided). Flush valves must deliver 35–75 litre min^{-1} of oxygen from the common gas outlet to atmosphere.

Oxygen supply failure precautions

There is a strong recommendation that all anaesthetic machines should have a primary audible alarm to indicate failure of oxygen supply and that this be powered solely by the oxygen supply pressure in the line between the cylinder pressure regulator or pipeline inlet and the flow control valve. It must be activated before this pressure decreases to 50% of the normal oxygen supply pressure or 180 kPa, whichever is the higher.

It is also recommended that a device should be fitted which is activated as above, and cuts off the supply of other gases to the patient or progressively reduces their flow whilst maintaining the proportion of oxygen. Such a "protection" device may also open the breathing system to atmosphere.

Overpressure valves

The current standard does not prescribe the use or performance of overpressure valves on the anaesthetic machine, but it is appreciated that there is a strong body of opinion in the U.K. that such a valve be fitted to the machine and be clearly marked with its opening pressure.

BREATHING SYSTEMS

Work on patient breathing systems is being undertaken and a standard is being developed which will specify the minimum performance and safety requirements of breathing systems and their components, with particular attention to resistance to gas flow, leakage and the arrangement of components in the circle absorber-type system.

OXYGEN ANALYSERS

A draft international standard for oxygen analysers for monitoring patient breathing mixtures is to be issued for voting and is likely to be published in the near future. This specifies requirements for the accuracy, alarm systems and safety of these devices and states the limits that interfering gases and vapours should have on their performance. The scope of this standard covers simple analysers for use in anaesthetic and ventilator breathing systems, paediatric incubators and perhaps in association with oxygen concentrators.

In some countries the use of an oxygen analyser in the breathing system is compulsory.

CONICAL FITTINGS AND ADAPTORS FOR BREATHING SYSTEMS

BS3849: 1965

The anaesthetic and intensive care applications of standards began in 1965, with the publication of BS3849. Before that time, metal breathing attachments, angle pieces, face masks, expiratory valves, etc., had generally been joined together by "push-fit" cone and socket joints and about a dozen different sizes were then in use. In every hospital, it was necessary to keep a large box of adaptors to permit connection of these various fittings. The British Standard specified 15-mm and 22-mm conical fittings for breathing system connections. Unfortunately, the introduction of the standard coincided with the development of new elastomeric materials so that, although the standard envisaged metal-to-metal connections, they were frequently made of hard rubber and fell apart. There was an additional problem of an excessive number of connections. Elastomeric (plastic) materials vary in their physical characteristics such as cold flow, creep and frictional properties, tolerance of temperature changes, and the effects of anaesthetic agents. The preference for single-use disposable elastomeric connections and the desire for cheap moulding has led to the production of plastic fittings which are outside the engineering tolerances of those used for metal. Plastic fittings made to engineering specifications for metal are more expensive and may occasionally still give unsatisfactory joints. New performance tests are therefore undergoing study in which the plastic component is engaged into a "test" male or female fitting with a specified axial force and rotation or torque. An analogous disengagement test is also being studied. These tests may require temperature and humidity conditioning and hence may prove to be complex, expensive and inappropriate.

The international standard for breathing attachments has therefore had a long gestation period, but will be issued as a draft for international voting in 1985.

Several studies have reviewed the frequency and causes of accidental breathing system disconnections (Cooper et al., 1978; Shaw, Davis and Anderson, 1982; Nuefeld and Johnson, 1983a, b). It is noteworthy that accidental disconnections occur at both 15-mm and 22-mm joints, and that many of the faulty fittings would not pass the gauging test described in BS3849. Nevertheless, it is likely that "anti-disconnect" fittings will be more frequently available. If the design of such fittings is simple, automatically applied when connections are made and yet facilitates easy disconnection, the devices will become more acceptable to anaesthetic and nursing staff.

There is no standard for "anti-disconnect" fittings, but the draft international standard describes a 22-mm screw-threaded fitting designed to support heavy or fragile breathing system components and yet permit easy engagement and disengagement by hand.

The increasing use of Anaesthetic Gas Scavenging Systems (AGSS) has led to the provision of 30-mm conical fittings for connection of transfer tubes of AGSS. A 19-mm fitting is also under consideration for this purpose. These sizes cannot be confused with 22-mm and 15-mm breathing system connections.

ANAESTHETIC GAS SCAVENGING SYSTEMS (AGSS)

The great difficulty in preparing an AGSS standard was the definition of the scope and purpose of such a document. If the intention was to prevent any pollution of the environment, the resulting costs would be enormous. The clinical implications would be that, in all patients anaesthetized with inhalation agents, the trachea must be intubated and high performance air conditioning must be used during patient transport and in recovery rooms. Initially, the U.S. National Institute of Occupational Safety and Hygiene (NIOSH) values were considered as possible targets by the technical committees, but there is little scientific evidence to support these values, and the legal implications are enormous. The current Draft International Standard concentrates on preventing damage to the patient which might be caused by AGSS. Particular attention is paid to expiratory resistance and positive or subatmospheric pressure on the breathing system. The performance of associated pressure relief valves is specified.

The British technical committee is studying the possibility of a national standard for active AGSS as the performance of passive systems is affected by several uncontrollable factors and thus they may not provide adequate protection against subatmospheric pressure being applied to the breathing system. The effect of different gas flows is also unpredictable and hence difficult to test.

OXYGEN CONCENTRATORS

The rapid development of oxygen concentrators results from their ability to provide a reliable and economical source of oxygen-enriched air. The technical committee has limited its work to those oxygen concentrators which are designed particularly for domiciliary use. Requirements for oxygen concentration, flow stability, outlet gas temperature, noise, particle content, electrical and fire precautions are being considered.

HUMIDIFIERS—BS4494: 1970

There have been many changes in humidifier design since BS4494:1970, and the current Draft International Standard includes new performance test methods. Particular emphasis is paid to "liquid output", delivered gas temperature, thermal safety and spillage protection. Detailed electrical requirements are taken from IEC Publication 601-1 and ISO2882, but specific clauses are included which amend or supplement 601-1.

A standard for heat and moisture exchangers is also under consideration.

VENTILATORS (BREATHING MACHINES)
BS3806: 1964

The main thrust of a ventilator standard is to describe methods of performance testing which ensure that ventilators deliver the appropriate volume of gas. These techniques were described by Sykes, Loh and Chakrabarti in 1978.

Unfortunately, so many changes are taking place in ventilator design and specifications that the Draft International Standard is already too limited in its scope. Work is continuing on this project.

RESUSCITATORS

Resuscitators are defined as small portable ventilators and hence should perform similarly to other ventilators. Several evaluations of resuscitator performance have demonstrated that many unsatisfactory devices are being marketed (Emergency Care Research Institute, 1971, 1979; Carden and Hughes, 1975; Carden and Friedman, 1977; Harber and Lucus, 1980; Health Equipment Information, 1983; Eaton, 1984).

The ISO technical committee is developing an international standard which provides specifications for the ventilatory performance of resuscitators in addition to their durability, reliability and tolerance of adverse environments.

TRACHEAL TUBES
BS3487: 1962, ISO5361 – PARTS 1 TO 5: 1984

The new international standard contains general requirements for trachael tubes and Parts 2, 3 and 4 describe particular requirements for Magill, Murphy and Cole types of tubes, respectively. Part 5 describes methods of testing tracheal tubes and cuffs, although kinking tests are still undergoing development. The standard specifies the internal diameter in the size designation, but there is provision for the external diameter to be marked on the tube. Also specified are basic dimensions of minimum tube length, cuff length and the distance between the patient end of the inflatable portion of the cuff and the nearest edge of the tube bevel (to minimize the hazard of the inflated cuff occluding the tube orifice).

There are also important international standards on tracheostomy tube and trachael tube connectors (BS6546: 1984, ISO7228: 1981).

ANAESTHETIC RESERVOIR BAGS
ISO5362: 1980

This standard specifies the neck design, size designation and electrical conductivity of anaesthetic reservoir bags.

OROPHARYNGEAL AIRWAYS
ISO5364: 1980

This standard includes specifications of size designations and basic requirements.

BREATHING TUBES—ISO5367: 1980

This standard covers basic requirements for breathing tubes, including electrical conductivity.

LARYNGOSCOPES
ISO7376, PARTS 1 & 2: 1984

These international standards describe basic requirements for the "hook-on" type of laryngoscope handle to blade fittings. Part 2 of the standard prescribes screw threads and sockets for laryngoscope bulbs.

A standard for fibrelight laryngoscopes is under development.

"ANAESTHETIC VOCABULARY"
ISO4135: 1979

A committee comprising some of the most articulate and widely read anaesthetists in the world achieved international agreement on this glossary of anaesthetic terms. The standard prefers "tracheal" tube to "endotracheal" and proscribes the use of "anaesthetic circuit" for a breathing system. However, the definition of "breathing system" has proved to be particularly difficult.

New equipment and techniques are being continuously introduced and therefore amendments and additions to this standard are expected.

The author recommends that people submitting papers for publication should consult this standard.

ELECTRICAL EQUIPMENT IN THE MEDICAL FIELD
IEC601-1 AND BS5724, PART 1: 1979

The electrical safety and performance of electrical equipment is under the purview of the International Electrotechnical Commission's Technical Committee No. 62. This organization has produced a long and complex standard, IEC601-1, which describes general requirements for the safety of medical equipment. It is likely that the general standard will be supplemented by separate particular standards for, for example, ventilators, anaesthetic machines, and other equipment. The particular standards take priority over the general standard.

Most IEC standards described requirements for electrical circuits and the prevention of electric shock including fault conditions, but IEC also cover fire, radiation and interference by high frequency equipment. Additionally, it deals with resistance to various environmental hazards such as equipment falling from a height, water-proofing and alarm signals, for example, when red or flashing red should be used.

Many IEC recommendations are not widely known to anaesthetists, and 601-1 is a difficult document in which to find information.

One section "Protection against the hazards of explosion in medically used rooms" defines three zones of explosive risk, based on the distance between a piece of electrical equipment and "the enclosed medical gas system", that is, the breathing system of a ventilator or anaesthetic machine, the patient's airways and any leak therefrom. The highest risk zone is that within the system or up to 5 mm around it, and electrical equipment suitable for use in this zone is to be classified as "Anaesthetic Proof Category G" and marked with a 2-cm wide green band imprinted with the letters APG. It has also to meet the most stringent requirements concerning electrical energy and insulation.

A lower risk "Anaesthetic Proof" zone is defined between 5 cm and 25 cm from the enclosed medical gas system. It must be marked with a green dot or circle imprinted with the letters AP.

The third zone is for equipment used more than 25 cm from the enclosed medical gas system and must be marked with an exclamation mark inside a triangle.

The instructions for use with anaesthetic machines not specified as category APG have to state that "as this machine is unsuitable for use with highly inflammable anaesthetic agents such as ether and cyclopropane, the use of antistatic tubing is unnecessary, moreover the use of antistatic or electrically conductive breathing tubes during surgery with high frequency electrical equipment may cause burns and is therefore not recommended in any application of this machine."

Criticisms of IEC are that clinicians are under-represented on its committees and its comprehensive standards incorporate many areas outside the electrical field and overlap with other standardizing organizations. In recent years the liaison between IEC and ISO has improved, and it is now hoped that the electrical aspects and functional performance of a piece of equipment can be harmonized into a single standard.

THE FUTURE

The proliferation of monitoring, measuring and therapy equipment which are each equipped with alarm and warning devices has led to a multiplicity of confusing and disturbing signals. Standards committees are exploring the possibility of limiting the number of alarm sounds and allocating levels of urgency of different types of signal.

Standards for transcutaneous oxygen and carbon dioxide monitors and other monitoring devices are likely to be developed in the near future.

APPENDIX

BRITISH STANDARDS INSTITUTION

British Standards Related to Anaesthesia and Intensive Care

BS3991: 1966	Doyen's mouth gag Gr 2.
BS5185: 1975	Dental vacuum pipeline service Gr 7.
BS3622: 1975	General purpose stools and anaesthetists chairs for hospital use Gr 5.
BS341:	Valve fittings for compressed gas cylinders Part 1: 1962 – Valves with taper stems (excluding valves used for breathing and medical purposes Gr 7. Part 2: 1963 – Valves with taper stems for use with breathing apparatus (excluding medical gas cylinders to BS1319) Gr 5.
BS691: 1979	Clinical maximum thermometers (mercury-in-glass) Gr 5.
BS896:	Stretchers and stretcher carriers Part 1: 1960 Dimensions Gr 2. Part 2: 1965 Performance Gr 2.
BS1263: 1946	Hypodermic syringes for use in medical and surgical practice Gr 5.
BS1319: 1976	Medical gas cylinders, valves and yoke connections (ISO/R32, 407) Gr 7.
BS1319C: 1976	Chart of colours for identification of the contents of medical gas cylinders Gr 1+VAT Unmounted; Gr 2+VAT Mounted and varnished.
BS2463: 1962	Transfusion equipment for medical use (+ISO1135) Gr 7.
BS2743: 1956	Sphygmomanometers. Aneroid type Gr 3.
BS2744: 1956	Sphygmomanometers. Mercury type Gr 3.
BS2891: 1957	Operating table covers or pads of cellular rubber Gr 3.
BS2904: 1957	Hospital sterilizers (boiling water type) Gr 6.
BS2927: 1957	Anaesthetic airway (+ISO5364) Gr 2.
BS3213: 1960	Hospital pressure sterilizers for water Gr 5.
BS3219: 1960	Horizontal cylindrical hospital sterilizers, pressure steam type Gr 5.

BS3220: 1960	Horizontal rectangular hospital sterilizers, pressure steam type Gr 5.
BS3233: 1960	Pressure steam sterilizers of small size (with independent steam supply) for unwrapped instruments and utensils Gr 3.
BS3353: 1961	Anaesthetic breathing bags made of anti-static rubber (+ISO5362) Gr 2.
BS3487: 1962	Endotracheal tubes Gr 4.
BS3522: 1962	Hypodermic surgical mounted needles (Luer fitting) (+ISO/R596) Gr 3.
BS3619: 1976	Mobile infusion stands Gr 2.
BS3806: 1964	Breathing machines for medical use Gr 6.
BS3849: 1965	Breathing attachments for anaesthetic apparatus Gr 4.
BS3930: 1965	Conical fittings with 6% (Luer) taper for hypodermic and other surgical equipment (+ISO/R594) Gr 3.
BS3970:	Steam sterilizers Part 1: 1966 Sterilizers for porous loads Gr 4. Part 2: 1966 Sterilizers for bottled fluids Gr 4. Part 5: 1968 Electrically heated steam generators for use with hospital sterilizers Gr 4.
BS3985: 1978	Cyanmethaemoglobin (haemoglobin–cyanide) solution for photometric haemoglobinometry Gr 3.
BS4005: 1977	Surgical rubber gloves (single use) Gr 3.
BS4199:	Surgical suction apparatus Part 1: 1967 Electrically operated surgical suction apparatus of high vacuum and high air displacement type Gr 4. Part 2: 1968 Electrically operated surgical suction apparatus for continuous drainage Gr 4.
BS4272:	Anaesthetic and analgesic machines Part 1: 1968 Anaesthetic machines of the on-demand type supplied with nitrous oxide and oxygen from separate containers Gr 3. Part 2: 1968 Analgesic machines of the on-demand type supplied with premixed nitrous oxide–oxygen from a single container Gr 2.
BS4316: 1968	Apparatus for measurement of packed red cell volume Gr 3.
BS4376: 1968	Electrically operated blood storage refrigerators Gr 5.
BS4494: 1970	Humidifiers for use with breathing machines Gr 4.
BS4843: 1972	Sterile intravenous cannulae for single use Gr 7.
BS4957: 1973	Specification for medical vacuum pipeline services for use in hospitals.
BS5081: 1976	Sterile hypodermic syringes and needles for single use Gr 7.
BS5616: 1981	Sterile intravascular catheters for single use Gr 5.
BS5682: 1984	Terminal units, hose assemblies and their connectors for use with medical pipeline systems.
BS5724:	Safety of medical electrical equipment Part 1: 1979 General requirements (+IEC 601-1) Gr 11.
BS5827: 1979	Mobile, manually operated patient-lifting devices Gr 3.
BS6155: 1981	Tracheal tubes for large animals in veterinary anaesthesia Gr 5.
BS6196: 1982	Sterile extradural catheters and their introducer needles for single use Gr 3.
BS2044: 1978	Laboratory tests for resistivity of conducting and anti-static rubbers (+ISO-1853) Gr 3.
BS2050: 1978	Electrical resistance of conducting and anti-static products made from flexible polymeric material Gr 4.
BS2782: 1970	Methods of testing plastics (+ISO/R117, 119, 120, 171, 181; +ISO/R62, 174, 292, 307) Gr 13.
BS2782:	Methods of testing plastics. Various parts. See Yearbook.
BS5736:	Evaluation of medical devices for biological hazards Part 1: 1979 Guide for the selection of biological methods of test Gr 3. Part 2: 1981 Method of testing by tissue implantation Gr 3. Part 3: 1981 Method of test for systemic toxicity; assessment of acute toxicity of extracts from medical devices Gr 3. Part 4: 1981 Method of test for intracutaneous reactivity of extracts from medical devices Gr 3.
BS5451: 1977	Electrically conducting and anti-static rubber foot wear (+ISO2024, 2251) Gr 3.
BS1710: 1975	Identification of pipelines (+ISO/R508) Gr. 7.
BS4778: 1979	Glossary of terms used in quality assurance (including reliability and maintainability terms) (+ISO3534. IEC271).
BS5750	Quality systems Part 1: 1979 Design, manufacture and installation Gr 3. Part 2: 1979 Manufacture and installation Gr 3. Part 3: 1979 Final inspection and test Gr 3. Part 4: 1981 Guide to use of BS5750: Part 1 "Design, manufacture and installation" Gr 7. Part 5: 1981 Guide to use of BS5750: Part 2 "Manufacture and installation" Gr 6. Part 6: 1981 Guide to use of BS5750: Part 3 "Final inspection and test" Gr 3.
BS5760: 1979	Guide to reliability programme management.
BS6000: 1972	Guide to use of BS6001. Sampling procedures and tables for inspection by Attributes (+ISO2859 ADD1) Gr 9.
BS6001: 1972	Sampling procedures and tables for inspection by attributes (ISO2859; +IEC) Gr 9.
BS6015: 1980	Glossary of terms used in anaesthesiology (=ISO4315) Gr 5.

ISO MEDICAL STANDARDS

ISO/R594–1967	3	Conical fittings for syringes, needles and other medical equipment – Definition and dimensional characteristics for conical fittings with a 6% and a 10% taper.
ISO/R595–1967	8	Syringes for medical use.
ISO6009–1981	3	Hypodermic needles for single use – Colour coding for identification.
ISO7864–1984	7	Sterile hypodermic needles for single use.
ISO7886–1984	13	Sterile hypodermic syringes for single use.
ISO4135–1979	17	Anaesthesiology – Vocabulary Bilingual edition.
ISO5358–1980	11	Continuous flow inhalational anaesthetic apparatus (anaesthetic machines) for use with humans.
ISO5362–1980	2	Anaesthetic reservoir bags.
ISO5364–1980	3	Oropharyngeal airways.
ISO5366/1–1980	2	Tracheostomy tubes – Part 1: Connectors.
ISO5367–1980	3	Breathing tubes used with anaesthetic apparatus and ventilators.
ISO7228–1981	3	Tracheal tube connectors.
ISO5361/1–1984	3	Tracheal tubes – Part 1: General requirements.
ISO5361/2–1984	7	Tracheal tubes – Part 2: Oro-tracheal and naso-tracheal tubes of the Magill type (plain and cuffed).
ISO5361/3–1984	2	Tracheal tubes – Part 3: Murphy type.
ISO5361/4–1984	3	Tracheal tubes – Part 4: Cole type.
ISO5361/5–1984	4	Tracheal tubes – Part 5: Requirements and methods of test for cuffs and tubes.
ISO7376/1–1984	18	Laryngoscopic fittings–Part 1: Hook-on type handle–blade fittings.
ISO7376/2–1984	3	Laryngoscopic fittings – Part 2: Miniature electric lamps – Screw threads and sockets.

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Br. J. Anaesth. (1985), 57, 718–721

CORRESPONDENCE

GYNAECOLOGICAL LAPAROSCOPY

Sir,—I was interested to read the findings of Drs Kurer and Welch (1984) in their investigations of techniques of anaesthesia for laparoscopy. I would like to make some comments.

Many studies have recommended the use of controlled ventilation, but even where spontaneous respiration was used, most investigators have used endotracheal intubation (Desmond and Gordon, 1970; Hodgson, McClelland and Newton, 1970; Lewis et al., 1972). There can be little doubt that the combination of Trendelenburg position and abdominal distension must predispose to passive gastric regurgitation. Some studies have shown an increased end-tidal carbon dioxide concentration during spontaneous respiration, and this has been associated with cardiac arrhythmias (Desmond and Gordon, 1970; Hodgson, McClelland and Newton, 1970). The potential dangers of aspiration, hypoventilation and cardiac arrhythmia are all decreased by tracheal intubation.

In the group which was under controlled ventilation, I would question the choice of pancuronium. In this series the duration of anaesthesia was, on average, 15 min or less. In these circumstances, the use of pancuronium, which has a medium to long duration of action, would seem undesirable (Martindale, 1977). It would seem more appropriate to consider the use of gallamine, or alcuronium, or better still one of the new non-depolarizing myoneural blockers, vecuronium or atracurium.

During the operation the authors noted that, in the spontaneously breathing group, some 18% had cardiac arrythmias. It is unfortunate that they did not evaluate whether this was of statistical significance, compared with the intubated and ventilated group. The authors applied statistical analysis to their other findings, and I wonder if such an analysis might not have shown that spontaneous respiration with a mask and breathing halothane was less than satisfactory during laparoscopy. My own analysis of a test of significance of proportions shows that the incidence of arrythmias is significant between the two groups ($P < 0.05$). Moreover, the "dysrhythmias" in the ventilated group were actually tachycardias of more than 120 beat min^{-1}, possibly attributable to the use of pancuronium. The true significance is therefore much higher.

In the recovery period there were four patients who suffered from respiratory problems, and all were in the controlled ventilation group. The clinical descriptions would seem to be entirely consistent with curarization. As no assessment of the degree of neuromuscular blockade was made, it will be impossible to confirm this. However, the dose of pancuronium used ($> 65\ \mu\text{g kg}^{-1}$) and the short duration of anaesthesia makes this at least a possibility.

I note that these women all had an invasive narcotic premedication, which not only caused complaints of dryness of the mouth, but must further have depressed respiration in the patients who breathed spontaneously, in addition to increasing the chance of nausea. I wonder if a more appropriate premedication might not be used to advantage (Beecher, 1955).

It would seem possible that the use of a short acting non-depolarizing relaxant might reveal that tracheal intubation and controlled ventilation is the method of safety and choice, with fewer respiratory problems after operation.

The combination of a narcotic premedication, spontaneous respiration with halothane, and using only a mask, may lead to complications in the hands of anaesthetists less experienced than the authors.

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Sir,—Thank you for giving me the opportunity to reply to Dr Lamberty's comments about our recent article. I acknowledge that his comment "there can be little doubt that the combination of the Trendelenburg position and abdominal distension must predispose to passive regurgitation" is accepted clinical teaching in anaesthesia. I would, however, like to draw his attention to some detail in the references that he cited.

The Trendelenburg tilt used by Hodgson, McLelland and Newton (1970) was 20° and was implemented for a period of at least 20 min. In the study of Lewis and associates (1972), the tilt was 30° maintained throughout the surgical procedure with a mean duration of 14.2 min. Desmond and Gordon (1970) were in an unfortunate situation in that the laparoscopies studied were of 30 min to 1 h duration and they used a 10–15° tilt. In our study we only used a 10° tilt and the surgical procedure lasted for a mean time of less than 5 min. Also, of the 120 patients we investigated, we were unable to demonstrate one case of passive gastric regurgitation. In a paper by Duffy (1979), two of 93 fasting patients did demonstrate this phenomenon in intubated cases, but in this study "the gynaecologist placed the patients in the lithotomy position with steep head-down tilt". I would, therefore, suggest that when the gynaecologist with expertise minimizes the physiological problems by requiring no more than 10° tilt and performs the procedure in less than 10 min, gastric regurgitation becomes less of a problem. I would, however, accept Dr Lamberty's sentiments in suggesting that, when the surgeon or anaesthetist, or both, are inexperienced, it is wiser to intubate the patient.

As regards the use of pancuronium, we did not intend to suggest that it is an ideal agent to produce neuromuscular blockade for this procedure, but were investigating two clinical techniques that had been used in the Royal Berkshire Hospital for many years and had satisfactorily fulfilled the requirements of both surgeons and anaesthetists. This also accounts for the choice of papaveretum and hyoscine premedication. I would agree that, for further clinical comparison of two such techniques, I would choose one of the newer agents as Dr Lamberty suggests, and monitor myoneural blockade with a peripheral nerve stimulator. Incidently, despite the invasive narcotic premedication, most of patients in our study required major analgesia after operation. Thus, I would be cautious about using benzodiazepine premedication without intraoperative opiates for inpatients.

The comments made about the statistical significance of cardiac arrhythmias are valid, but I do not see that it can be presumed that the tachycardias could just be attributable to the use of pancuronium, as the stress of tracheal intubation readily produces such changes. Harris, Plantevin and Crowther (1984) have demonstrated that, in laparoscopy patients during intubation facilitated by suxamethonium and topical 4% lignocaine to the vocal cords, 16% developed arrhythmias. Furthermore, for the duration of abdominal insufflation there was no statistical difference in the incidence of arrhythmias between the group which were ventilated with alcuronium and halothane and the group of patients who breathed spontaneously on enflurane.

In summary, I agree with the penultimate paragraph of Dr Lamberty's letter, but if laparoscopy is to be seriously considered as a day-case procedure, the significantly better morbidity at 4 h in our non-intubated patients breathing spontaneously should be further investigated. I await the results of a study that compares the technique rationally advocated by Dr Lamberty with a technique in which patients are not intubated and breathe spontaneously under the conditions as described in our article.

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RELATIVE POTENCY OF AGONIST AND PARTIAL AGONIST OPIOIDS

Sir,—The use of relative potency when comparing agonist with partial agonist drugs may be misleading. Partial agonists have flatter log dose–response relationships than full agonists, and with non-parallel curves a relative potency can only refer to a single level of response, for example point A in figure 1. At any other level, the relative potency must be different. With doses producing greater response (points B), the ratio partial agonist:agonist is inevitably increased.

It is, therefore, inappropriate to apply a relative potency derived in one set of circumstances in a different situation, unless it can be shown that the same level of effect is achieved in both instances. In their paper comparing the respiratory depressant effects of meptazinol and pethidine, Slattery and colleagues (1983) may have concluded incorrectly that, in the doses tested, there is no advantage of meptazinol over pethidine in respect of respiratory depression "since the equipotent dose ratio for analgesia is 2.4:1". It is impossible to compare levels of response in the widely differing circumstances in which this ratio was determined (using on-demand analgesia) and applied.

In addition, the use of on-demand analgesia to determine relative potency of analgesics (Slattery et al., 1981; Harmer et al., 1983) is full of pitfalls. A retrospective assessment of a variable degree of pain is an unreliable method of assessing level of effect, especially if it is uncontrolled in relation to recent opiate medication; also, the ratio of doses of drugs used over 24 h, which are affected by drug, duration of effect and cumulation, is irrelevant to single dosage.

Where partial agonists are concerned, the method is liable to introduce numerically large errors. When the effects sought are on the linear part of the dose–response curve, the relatively flat relationship means that considerable changes in dosage cause limited changes in effect. Thus small, statistically insignificant differences in mean pain score may reflect large differences in dose. Also, when patients, in an effort to achieve more analgesia, use doses greater than the smallest producing maximum effect (point C, fig. 1), the dose bears no relationship to the analgesia obtained, and the relative potency derived is worthless. This may possibly occur with partial agonists of low maximum efficacy. Finally, the patient's assumption of satisfactory analgesia, the pain score indicated and the amount of analgesic used may all be affected by side effects produced.

It is not surprising, therefore, that Slattery and colleagues' potency ratio of 2.4:1 for meptazinol and pethidine differs so widely from Paymaster's (1977) assessment of equipotency at a dose of 100 mg. Paymaster's patients obtained adequate analgesia at this dose, but Slattery's, who had undergone major upper abdominal surgery, may well have sought a greater effect. The same group (Harmer et al., 1983) determined a different potency ratio, of 1.39:1, for the two drugs used in patients after similar surgery, which may reflect a lower level of analgesia achieved by

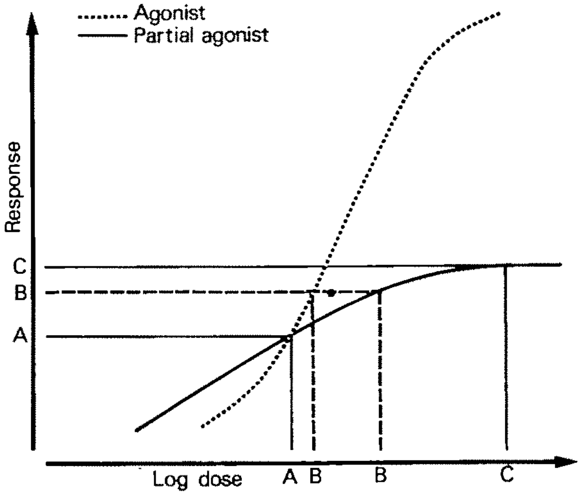

FIG. 1. Schematic log dose–response relationships for agonist and partial agonist drugs.

i.m. instead of i.v. infusion. However, their results in no way justify their statement that meptazinol is "less potent than pethidine". The slightly greater rate of use of meptazinol produced a mean pain score of 38 as opposed to 52 for the patients who received pethidine. Indeed, meptazinol may well be more potent than pethidine in doses smaller than 100 mg.

It is obviously essential that relative potency should be related to a single dose, or level of response, but it is incorrect to use the method of Harmer and co-workers (1983), who related doses of morphine, buprenorphine and meptazinol to pethidine 100 mg. As these relationships were obtained by division of 24-h dosage, they may bear no resemblance to those obtaining at the level of response to pethidine 100 mg. These relative potencies should, like others, only be used in the context in which they were obtained.

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Sir,—Dr Kay schematically illustrates an aspect of theoretical analgesia receptor pharmacology. His thesis would have been more convincing with real data, but these may be hard to find. Our experience with meptazinol for severe postoperative pain by self-administration showed it to be significantly less potent than pethidine. We agree that it is probably also less efficacious than pethidine (in the way Dr Kay's diagram shows) because, although mean analogue scores for pain were not significantly different, some patients who received meptazinol withdrew from the trial, while none of those receiving pethidine did so.

It is not clear whether Dr Kay is quoting from unpublished data, giving an opinion, or merely extrapolating from the theoretical dose–response curves when he goes on to assert that meptazinol may be, *per contra,* more potent than pethidine at doses equivalent to less than 100 mg of pethidine. In any event, not many clinicians are interested in the relative potency of barely therapeutic doses. Furthermore, Dr Kay does us less than justice by selective quotation. We did not say that meptazinol "is less potent than pethidine" but that "in these terms . . ." (rate of consumption) ". . . it is less potent than pethidine, although it seems relatively more effective when given intramuscularly . . ."

Dr Kay maintains that relative potency should be related to a single dose or level of response. That was so in our study. The *response* was obtained when the patient titrated himself to optimum analgesia with the study drug, balancing pain relief against side effecs. Each patient was at liberty to keep pain relief optimal all the time.

Dr Kay is probably correct in saying that equipotency ratios for analgesia should not be compared with the effects of a single dose on respiration. However, most patients receive multiple doses of analgesics, so that the practical question is whether a range of different prescribed doses could have effects on ventilation akin to the agonists pethidine and morphine. This seems at least *possible.*

Dr Kay alleges that comparing potency by a patient demand technique is generally unreliable. However, determinations of equivalent potency for buprenorphine and pentazocine (Slattery et al., 1983) pethidine and meptazinol (Slattery et al., 1981) and now morphine, pethidine and nalbuphine (Bahar, Rosen and Vickers, 1984), fall within generally accepted ranges. The consistency shown does not support the view that estimates based on self-administered regimens are "full of pit-falls". It is possible that meptazinol is the exception and some of the problems may lie in its lack of efficacy. In a small study of 10 mothers in labour, using self-administration by the i.m. route, meptazinol was 1.5 times less potent than pethidine, and three of five mothers receiving meptazinol asked for an extradural block in future: none of the five receiving pethidine did so.

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BRONCHOSPASM AND HYPOTENSION FOLLOWING CARDIOPULMONARY BYPASS

Sir,—The case of bronchospasm and hypotension following cardiopulmonary bypass reported by Drs Durant and Joucken (1984) raises several interesting points.

The authors describe the rarity of this phenomenon, with a reported incidence of four cases worldwide. In the recent experience of this hospital there have been three cases of sudden massive increase of airway pressure (>40 cm H_2O) in a series of 90 bypass procedures. None of these patients had a history of allergy or asthma. This incidence of 1 in 30 would imply that perhaps the condition is not all that rare.

The description of this increased airway pressure as bronchospasm would imply an underlying bronchomotor abnormality. This issue is clouded by the use of drugs such as aminophylline and adrenaline, which have profound cardiovascular and bronchomotor effects. So many factors are changing at the end of cardiopulmonary bypass that a simple cause may be hard to find. This was particularly true of our second patient, in whom no cause was found, the "bronchospasm" improving gradually with aminophylline and adrenaline. However, in our other two patients a specific cause was found or implied. In the first, the occurrence of an increase in airway pressure and hypotension responded to the removal of a swab placed under the left atrium; that is, the condition was caused by acute pulmonary venous congestion. In the third patient, the increase in airway pressure and deterioration in cardiac output were accompanied by a decrease in arterial oxygen saturation. The $P\text{O}_2$ was maintained at 10 kPa only by use of $F\text{I}_{\text{CO}_2}$ 1.0 and PEEP 10 cm H_2O. This patient responded slowly to a combination of antihistamine, aminophylline and adrenaline, and the cessation of protamine administration. It was considered that this patient was demonstrating a reaction to protamine (Best et al., 1983) or the protamine–heparin complex (Best et al., 1984).

It is, therefore, worth noting that bronchospasm after cardiopulmonary bypass is not a rare condition and that several causes may exist. The fact that so many cardiovascular and respiratory variables are occurring at this time makes investigation of this phenomenon extremely difficult.

P. A. J. HARDY
Edinburgh

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—— Teisner, B., Grudzinskas, J. G., and Fisher, M. M. (1983). Classical pathway activation during adverse response to protamine sulphate. *Br. J. Anaesth.*, 55, 1149.

Sir,—I do agree with Dr Hardy that the incidence of increased bronchomotor activity at the completion of cardiopulmonary bypass may be grossly underestimated. As mentioned in the first part of the discussion, numerous factors modifying airway reactivity during bypass may lead to "bronchospasm". Only the most severe cases are likely to be reported.

Moreover, the vasodilatation without phenylephrine in a patient pretreated with labetalol, a competitive alpha- and beta-adrenoceptor antagonist, may be meaningful and should stimulate anaesthetists to search for similar interaction. In addition to the role played by cimetidine, genetic polymorphism in the oxidative metabolism of beta-adrenoreceptor antagonists, such as metoprolol, propranolol, timolol and alprenolol, is largely responsible for individual differences in their plasma concentrations and antihypertensive effects (Lennard et al., 1982). The prevalence of the poor hydroxylator phenotype is about 9% in the United Kingdom, but it varies widely among ethnic groups, from 1% in Arabs to 30% in Hong Kong Chinese. Genetic polymorphism in the metabolism of labetalol, although not demonstrated, is likely. In the present case, shortness of breath with wheezing occurred after 1 week of therapy with metoprolol 100 mg day^{-1} by mouth. In addition, hypotension and bronchospasm were observed during bypass after preoperative infusion of labetalol 600 mg. The role of genetic polymorphism in the metabolism of beta-adrenoceptor antagonists, although questionable in this patient, is worthy of mention and deserves evaluation.

P. A. C. DURANT
Rochester

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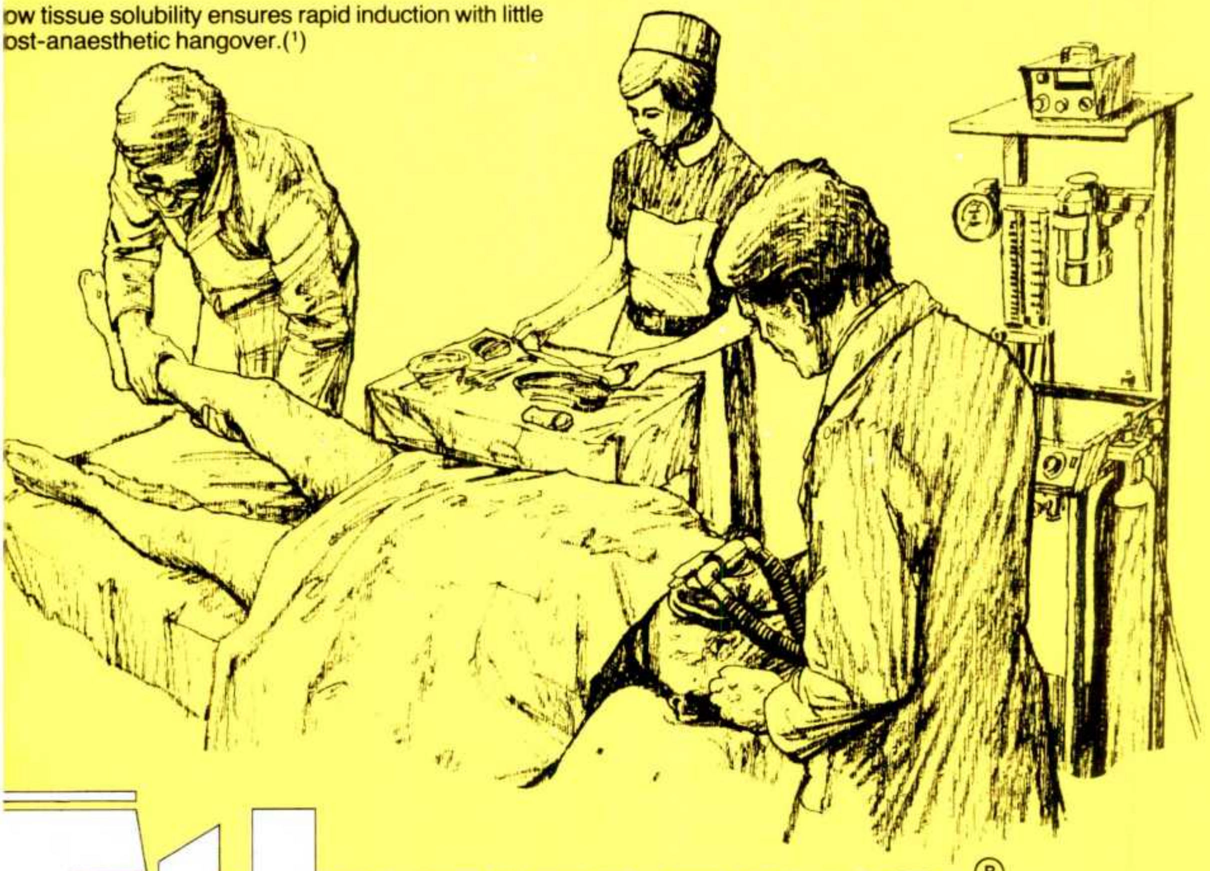

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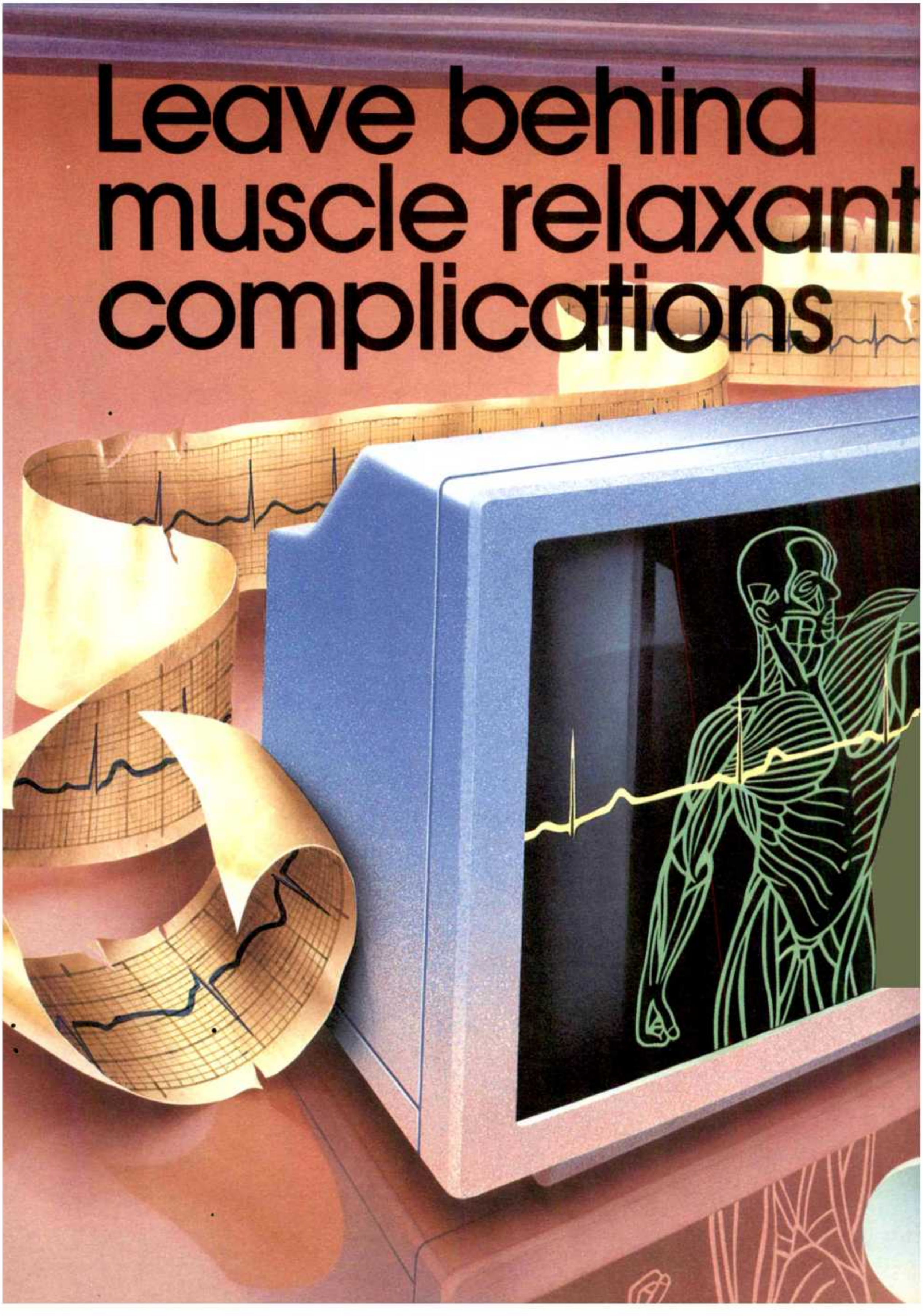
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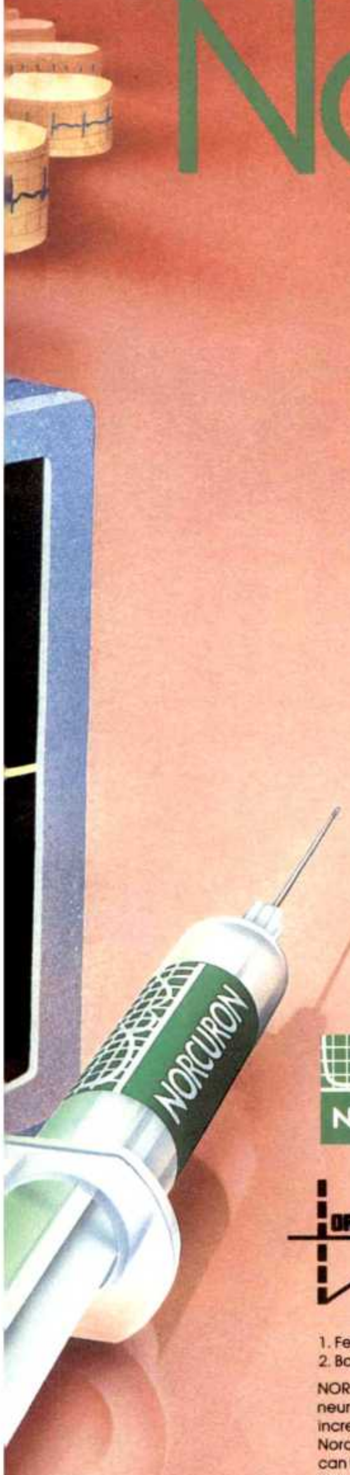

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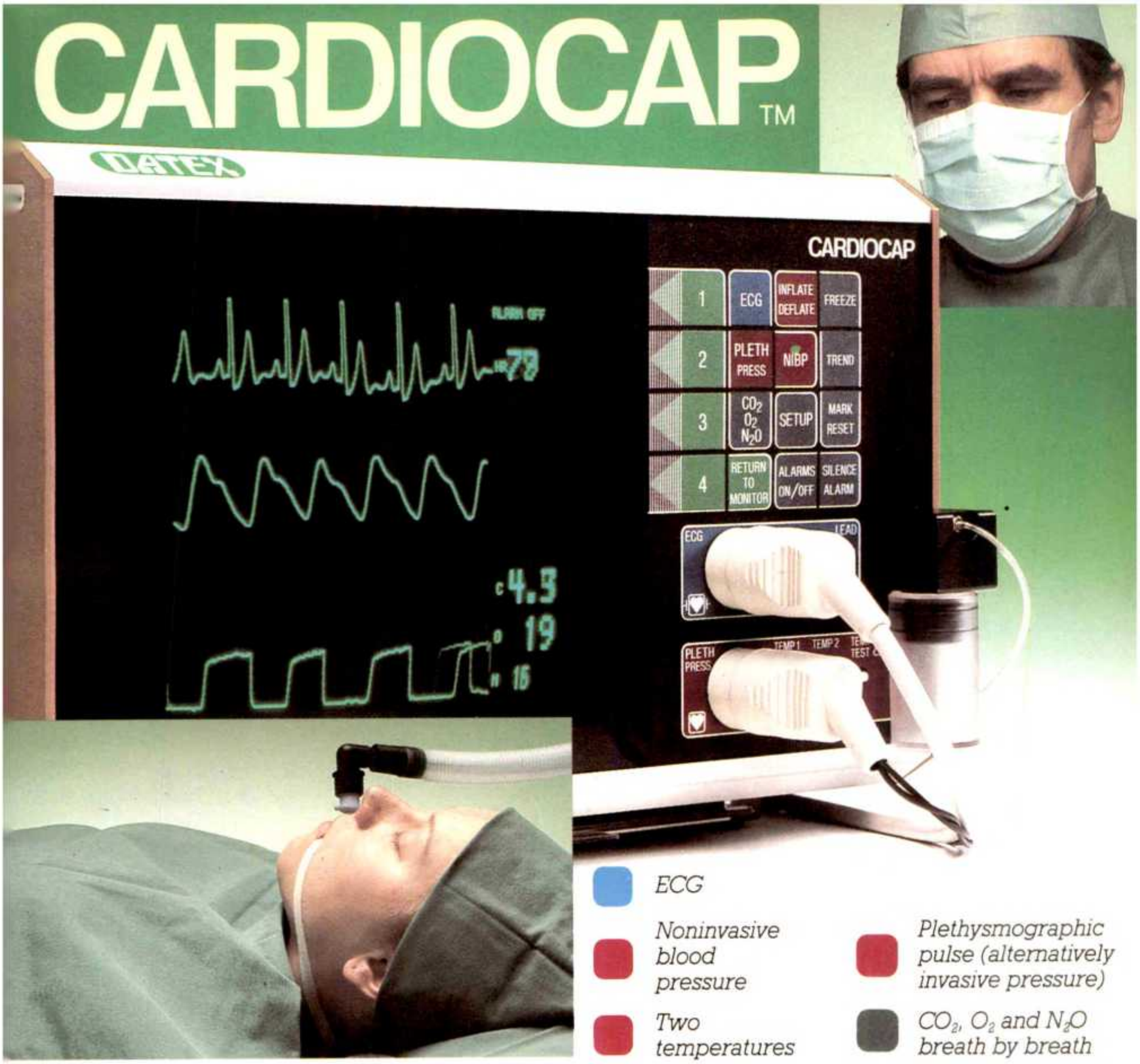

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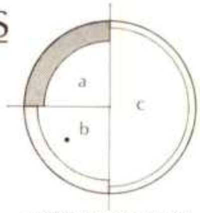

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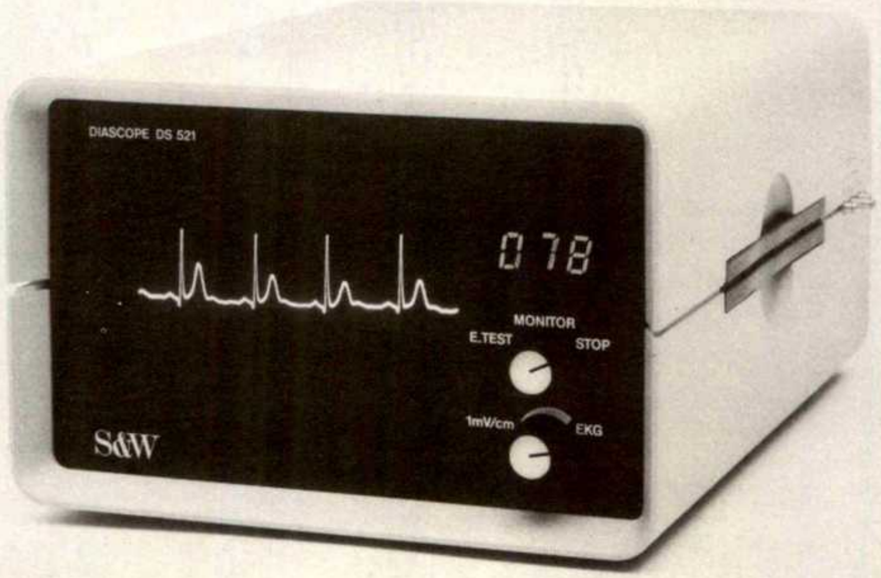

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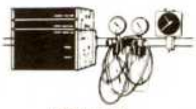
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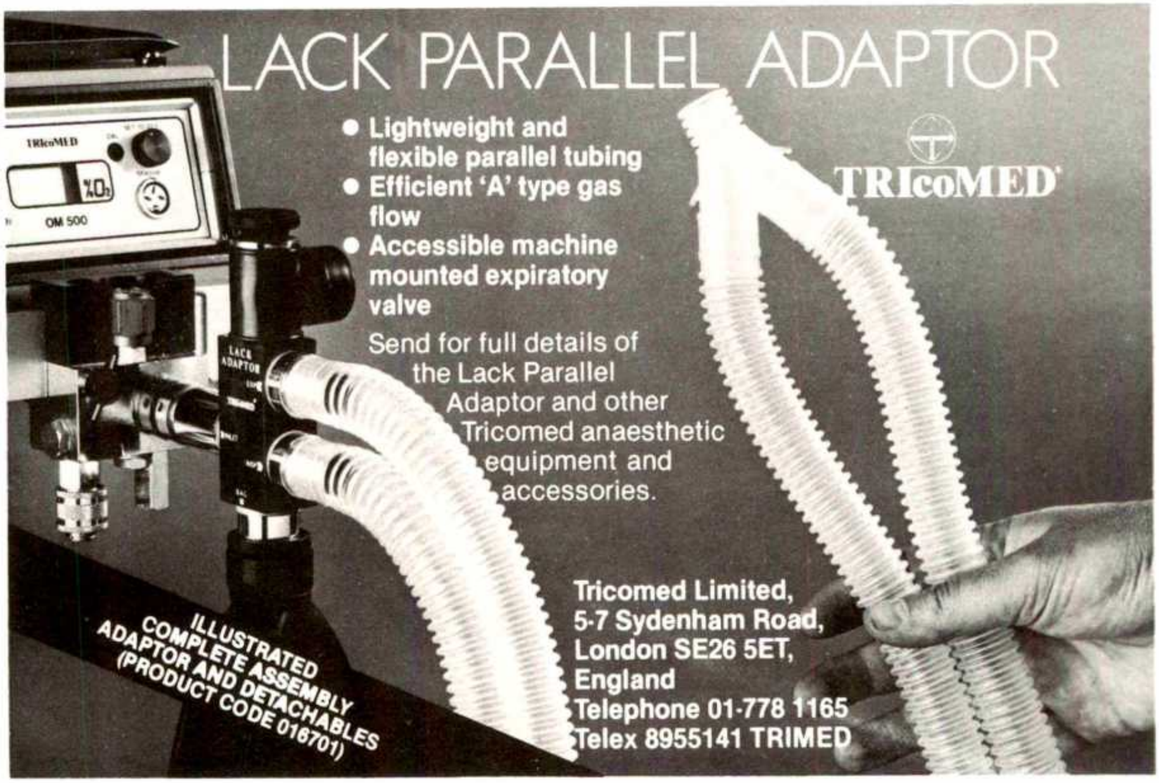
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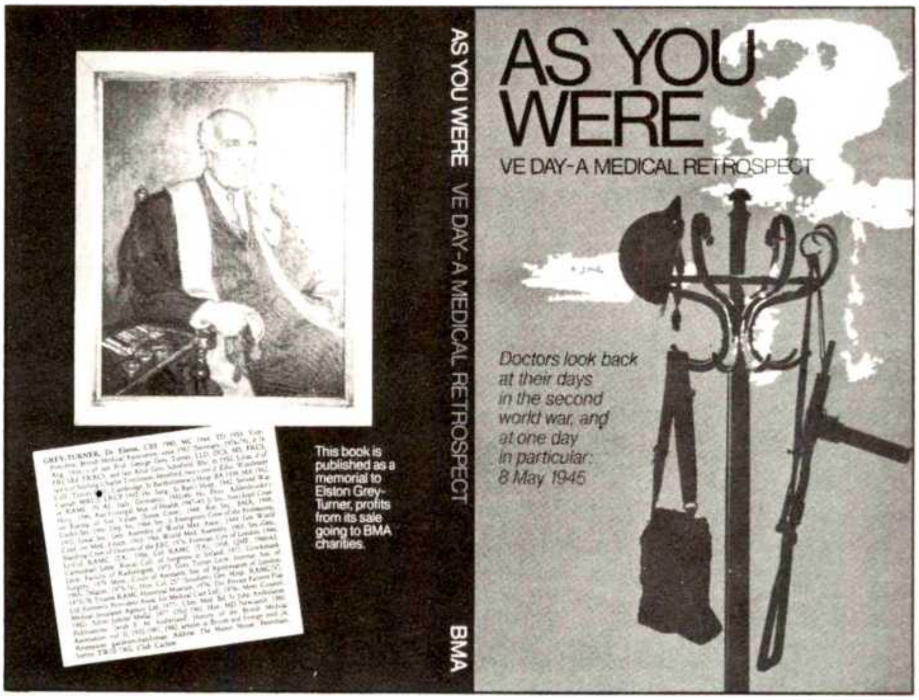
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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 57, No. 9 SEPTEMBER 1985

EDITORIAL

EVOKED RESPONSES—A NEUROPHYSIOLOGICAL INDICATOR OF DEPTH OF ANAESTHESIA?

The introduction of balanced anaesthetic techniques involving the use of neuromuscular blocking drugs has made the assessment of the depth of anaesthesia more difficult, because respiratory pattern and spontaneous movement are no longer available as signs of inadequate anaesthesia. Assessment of the depth of anaesthesia is now carried out by monitoring the autonomic responses to surgery, but this is not wholly satisfactory as demonstrated by an incidence of awareness during balanced techniques. Furthermore, these responses may be modified by a variety of drugs in increasingly common usage, for example beta-blocking agents. Alternative approaches which have been proposed include scoring systems based on traditional vital signs, the isolated forearm technique, spontaneous and evoked lower oesophageal contraction, integrated frontalis EMG and skin resistance (Evans and Davies, 1984). None of these has achieved routine acceptance, although oesophageal contraction techniques have not been fully evaluated as yet. More direct measures of central nervous activity utilizing electroencephalography (EEG) have also been investigated but have been found generally unsatisfactory because changes are agent specific, difficult to interpret, and show wide inter-patient variations. Methods of automated analysis of the EEG have also received interest, for example the cerebral function monitor (CFM), cerebral function analysing monitor (CFAM), compressed spectral array, power spectral edge and aperiodic analysis, but these also suffer from the basic objections stated above.

Before discussing the potential applications of evoked responses, we should define the requirements of an indicator of depth of anaesthesia. It should show graded responses to changing depth of anaesthesia at all levels from light sedation to deep surgical anaesthesia. It should be independent of anaesthetic technique and respond to surgical stimulus when anaesthesia is inadequate. The indicator should be easily quantified, readily interpreted, and be unaffected by such routine operating theatre interference as electrocautery.

We have been interested in the application of specific central nervous system evoked responses to this problem. These responses can be easily obtained by repetitive presentation of a suitable stimulus whilst simultaneously recording the EEG signal from scalp electrodes. This signal is amplified, digitized, then averaged on line using a computer technique, thus selectively enhancing the stimulus-related EEG and eliminating unrelated background activity. The most practical techniques in common neurophysiological use involve stimulation of visual, auditory and somatosensory pathways. They have been shown to be applicable to operating theatre use for monitoring regional ischaemia during neurosurgery (Grundy, 1983).

The potential application of evoked responses to monitor depth of anaesthesia has been demonstrated by Uhl and colleagues (1980). Increasing concentrations of halothane were shown to produce graded increases in the latency of the first major positive potential (P1) of the cortical visual evoked response. Since then we and our colleagues have systematically studied the effects of a wide variety of anaesthetic agents on the three modalities of evoked response. In doses in the clinical range, the inhalation agents, halothane, enflurane and isoflurane all increase latencies of the early (brainstem) and middle latency components of the auditory response and reduce the amplitude of the middle latency components (Thornton et al., 1983; Thornton et al., 1984; Navaratnarajah et al., 1985; Sebel et al., 1985). Isoflurane also increases the latency and decreases the amplitude of the cortical somatosensory and visual evoked responses (Sebel et al., 1985). Nitrous oxide given alone in concentrations up to 50% decreases the

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amplitude of cortical somatosensory and visual evoked responses, but has no effect on latency of the cortical somatosensory, visual or brainstem auditory components (Sebel, Flynn and Ingram, 1984). Althesin and etomidate have a similar effect on the middle latency components to the halogenated agents but have no effect on the brainstem responses (Navaratnarajah et al., 1983; Heneghan et al., 1984). Other workers have demonstrated that fentanyl 50 $\mu g\ kg^{-1}$ has no effect on brainstem responses (Samra et al., 1984). These results confirm previous observations that brainstem responses are robust, and even with the halogenated agents the changes seen were of small magnitude. They are therefore of limited application to measurement of depth of anaesthesia. However, the cortical components of all three stimulus modalities are profoundly affected by all drugs studied in a graded, reversible and non-agent-specific manner. As such they hold promise as measures of depth of anaesthesia.

Further work is required before these techniques can be shown to fulfil our ideal criteria. First, although we have shown graded changes with changing anaesthetic concentration, we have not yet established any relationship with the patient's response during surgery. This may prove difficult as there is no standard reference for depth of anaesthesia for comparison. Second, interpretation of recordings of evoked responses requires some training in identifying the various components, particularly when signal-to-noise ratio is low, as may occur during deep anaesthesia. However, future advances in automated peak identification may obviate this problem. Third, the effect of temperature should be considered. Hypothermia increases latency and decreases amplitude in a manner similar to anaesthetic agents, although it is not clear whether this is related to the anaesthetic effects of hypothermia or merely to a physical effect on central nervous conduction. Finally, we must consider the effects of drug mixtures. Most studies have involved the effect of a single drug, so that little is known about the effects of drug interactions and whether mixtures are additive or whether synergism occurs.

The final index that is used for anaesthetic evoked response monitoring may need to be a function of both latency and amplitude. When these points have been resolved, evoked response measurements should provide a convenient and reliable neurophysiological indicator of depth of anaesthesia.

P. S. Sebel, C. P. Heneghan
and D. A. Ingram

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CEREBRAL ELECTRICAL ACTIVITY INFLUENCES THE EFFECTS OF ETOMIDATE ON CEREBRAL PERFUSION PRESSURE IN TRAUMATIC COMA

R. M. BINGHAM, F. PROCACCIO, P. F. PRIOR AND C. J. HINDS

SUMMARY

The effects of 124 boluses of etomidate 0.2 mg kg^{-1} i.v. on intracranial pressure (ICP), mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) were studied in eight patients with severe head injury (Glasgow coma score < 8). The data were divided into two groups based on the minimum voltage of the cerebral function monitor (CFM) recording before the bolus. In group A this was less than $5\,\mu V$ (representing profound cortical electrical depression), while in group B the minimum voltage was greater than $5\,\mu V$. The mean decrease in ICP following etomidate was significantly greater in group B (mean ± SEM: -8.6 ± 0.7 mm Hg) than in group A (-3.8 ± 0.6 mm Hg) ($P < 0.0001$). The decrease in arterial pressure was similar in both groups. Consequently, there was a small mean increase in CPP in group B (2.2 ± 0.9 mm Hg), whereas in group A CPP decreased (-4.7 ± 1.5 mm Hg) ($P < 0.001$). There was a strong correlation between the decreases in ICP and MAP in group A ($r = 0.70$, $P < 0.01$), but not in group B ($r = 0.05$). Thus, when cortical electrical activity was already maximally suppressed, further administration of an i.v. anaesthetic agent produced only relatively small decreases in ICP, largely as a passive response to decreases in MAP. CPP was therefore usually reduced. Conversely, in the absence of such depression larger decreases in ICP, unrelated to hypotension, occurred and these were usually associated with increases in CPP. However, even under these circumstances, potentially dangerous decreases in CPP may be seen.

Prevention of secondary ischaemic insults in patients in traumatic coma is based on minimizing cerebral metabolic demands and maintaining adequate cerebral perfusion by controlling intracranial pressure (ICP) and optimizing systemic arterial pressure (Moss et al., 1983). Methods currently used to control ICP include the administration of osmotically active agents, diuretics and, less frequently, steroids as well as artificial ventilation. Many centres have also used continuous infusions of i.v. anaesthetic agents, supplemented if necessary, by bolus doses to decrease acute increases in ICP or to prevent increases in ICP in response to stimulating procedures (Moss, Gibson and McDowall, 1980; Prior et al., 1983). Unfortunately, these agents can also depress the cardiovascular system (Traeger et al., 1983) and, consequently, the net effect on cerebral perfusion pressure (CPP) is variable and depends on the relative magnitude of the alterations in ICP and mean arterial pressure (MAP). Thus although the administration of bolus doses of i.v. anaesthetic agents to patients with intracranial hypertension can decrease ICP, on occasions potentially dangerous decreases in CPP can occur (Prior et al., 1983). Clearly, therefore, it would be advantageous to be able to predict in an individual patient the probable effects of such therapy on ICP, MAP and CPP.

Since the reduction of ICP produced by these agents is related to a decrease in cerebral blood

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flow (CBF), which is, in turn, a response to a reduction in cerebral metabolic requirements (cerebral metabolic rate for oxygen, $CMRo_2$) (Pickerodt et al., 1972; Sari et al., 1976; Renou et al., 1978), the effect is likely to be least when neuronal metabolism is already significantly depressed. We have investigated the relationship between cerebral metabolic rate, as reflected by cortical electrical activity (Paulson and Sharbrough, 1974) monitored using the cerebral function monitor (CFM) and the changes in ICP, MAP and CPP occurring in response to the i.v. administration of bolus doses of etomidate.

PATIENTS AND METHODS

Patients

Eight consecutive patients (two female) admitted to the Intensive Care Unit with severe head injury (Glasgow Coma Score < 8) were studied. Their ages ranged from 3 to 37 yr. Evacuation of an intracranial haematoma was performed in three patients (one intracerebral, one extradural, one subdural). Four had diffuse swelling and the remaining patient had, predominantly, oedema of the left hemisphere.

Monitoring

Indwelling Teflon cannulae in a radial artery and in the right internal jugular vein were used to permit the continuous monitoring of arterial and central venous pressures (CVP), respectively (Bell & Howell type 4/327/1 pressure transducers).

A pre-calibrated subdural pressure transducer (Gaeltec Ltd) was used for the continuous measurement of ICP, and the electroencephalograph (EEG) was recorded continuously using a Cerebral Function Monitor (Par Medex Ltd). Three scalp needle electrodes were used in standardized left and right parietal positions with a mid-frontal "guard" electrode to help rejection of interference. All monitoring equipment was calibrated at least twice a day, and more frequently if necessary.

A continuous record of CVP, MAP, ICP and cerebral electrical activity was obtained on a Devices M19 4-channel chart recorder.

Treatment

All patients received intermittent positive pressure ventilation to maintain Pa_{CO_2} between 3.4 and 4.7 kPa. Inspired oxygen concentration was adjusted to maintain arterial oxygen saturation greater than 90%.

Patients were sedated with a continuous infusion of etomidate (initially 5 $\mu g\ kg^{-1}\ min^{-1}$ i.v.) and intermittent opiates (usually phenoperidine 1–2 mg i.v.). Pancuronium 2–4 mg i.v. was administered if necessary to prevent the patient resisting the ventilator.

If the ICP increased to more than 20 mm Hg, further etomidate was administered, either as a bolus (0.2 mg kg^{-1}) or by increasing the rate of the infusion (up to 25 $\mu g\ kg^{-1}\ min^{-1}$). Mannitol (0.3 g kg^{-1}) was also used to control ICP. However, if on any occasion the ICP failed to decrease following mannitol, its use was discontinued and frusemide 20 mg i.v. followed by acetazolamide 250 mg i.v. 6-hourly was substituted. All but one patient received a dose of mannitol at some stage during their treatment, although only four required additional administrations.

Fluid intake was restricted to 5% dextrose 1 ml $kg^{-1}\ h^{-1}$. Colloidal solutions (Haemaccel or plasma protein fraction) were administered as required to maintain circulating volume.

Prophylactic anti-convulsant therapy (phenobarbitone 60 mg i.m. 8-hourly in adults) was given to all patients (supplemented with diazepam and phenytoin if seizures occurred).

Essential stimulating procedures (physiotherapy, tracheal suction) were preceded by the administration of a bolus of etomidate 0.2 mg kg^{-1} to attenuate the associated increase in ICP.

All events, drug administrations and procedures were noted on the four-channel chart recording, which was continued for the duration of ICP monitoring (up to 7 days).

The effects of bolus doses of etomidate were measured by retrospective analysis of the chart records by one author (R.B.). Random and independent checks of consistency were made by another (F.P.). Analysis was restricted to the 124 occasions on which the bolus of etomidate was not accompanied by the administration of any other drug(s), and during which no stimulating procedure had occurred.

The data were divided into two groups on the basis of the minimum voltage of the CFM trace immediately preceding the bolus. Either (group A; $n = 29$ observations obtained in five patients) this was depressed to 5 μV or less (representing marked reduction in cortical electrical activity) or (group B; $n = 95$ observations obtained from eight patients) CFM minimum voltage was greater than 5 μV. This value was chosen to discriminate between the two groups as it represents a profound decrease in cerebral electrical activity, which has been shown by previous work to correspond to a "burst suppression" pattern on the conventional EEG (Prior, Maynard and Brierley, 1978).

The measurements made and the derivation of the calculated values are shown in the appendix. The Pearson product–moment correlation and the two-sample *t* test were used for statistical analyses.

RESULTS

Baseline values of ICP did not differ significantly between the two groups (table I). Although the pre-bolus MAP was slightly lower in group A (mean ± SEM: 73.9 ± 3.1 mm Hg) than that in group B (81.5 ± 1.6 mm Hg) ($P = 0.04$) (table I), there was no significant difference in the decrease in MAP following etomidate in the two groups (group A: −8.4 ± 1.9 mm Hg; group B: −6.4 ± 0.7 mm Hg) (table II). The administration of etomidate decreased ICP on 90% of occasions in group A and 97% in group B. However, the magnitude of the decrease was significantly greater in group B (−8.6 ± 0.7 mm Hg) than in group A (−3.8 ± 0.6 mm Hg) ($P < 0.0001$) (table II, fig. 1). Since the mean decrease in MAP was similar in both groups, the larger reduction in ICP in group B resulted in a small mean increase in CPP (2.2 ± 0.9 mm Hg) whereas, in group A, the boluses of etomidate produced a mean decrease in CPP (−4.7 ± 1.5 mm Hg) (table II, fig. 1). These differences in CPP following the boluses were significant ($P < 0.001$).

TABLE I. *Pre-bolus values (mean ± SEM) of MAP and ICP in groups A (CFM < 5 μV) and B (CFM > 5 μV). Two-sample* t *test*

	Group A (CFM < 5 μV)	Group B (CFM > 5 μV)	*P*
Pre-bolus MAP (mm Hg)	73.9 (±3.1)	81.5 (±1.6)	0.04
Pre-bolus ICP (mm Hg)	21.0 (±1.3)	21.6 (±0.7)	ns

TABLE II. *Change in MAP, ICP and CPP (mean ± SEM) following etomidate boluses (0.2 mg kg^{-1}) in groups A (CFM < 5 μV) and B (CFM > 5 μV). Two-sample* t *test*

	Group A (CFM < 5 μV)	Group B (CFM > 5 μV)	*P*
ΔMAP following bolus (mm Hg)	−8.4 (±1.9)	−6.4 (±0.7)	ns
ΔICP following bolus (mm Hg)	−3.8 (±0.6)	−8.6 (±0.7)	< 0.0001
ΔCPP following bolus (mm Hg)	−4.7 (±1.5)	+2.2 (±0.9)	< 0.001

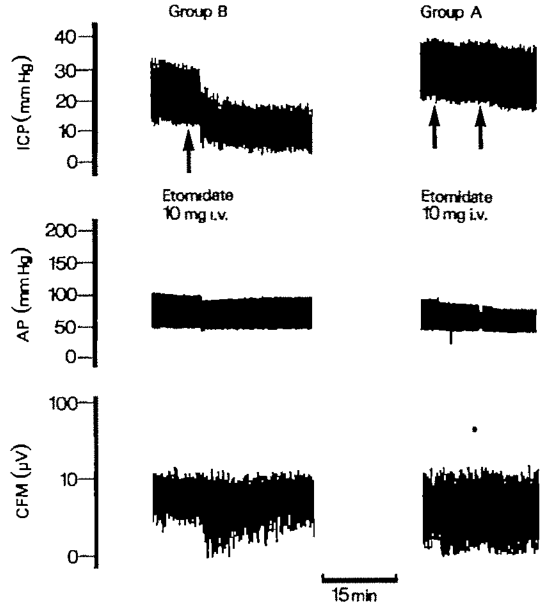

FIG. 1. Examples of effects of etomidate boluses on ICP, arterial pressure and CFM voltage in groups A and B. On the left, CFM minimum voltage was greater than 5 μV before the etomidate bolus (group B). Administration of the bolus resulted in a marked decrease in ICP (associated with a decrease in the minimum CFM voltage to less than 5 μV). Arterial pressure decreased also, but to a lesser extent; CPP was therefore increased. On the right is an example from the same patient 6 h later, but in this instance the CFM was depressed below 5 μV before the bolus (group A). Administration of the same dose of etomidate had minimal effect on ICP; a similar decrease in arterial pressure therefore resulted in a decrease in CPP.

Although mean CPP increased in group B, the effects of individual boluses were variable (table III). In this group CPP decreased following 38% of the etomidate boluses, and remained unchanged in 3%. In group A CPP usually decreased (69% of occasions), although on 14% of occasions it remained unchanged (table III).

The maximum increase in CPP was only 6 mm Hg in group A (this was secondary to an increase in MAP of 5 mm Hg rather than a reduction in ICP), whereas in group B an increase in CPP of greater than 6 mm Hg occurred following 30% of the administrations of etomidate,

TABLE III. *Effects of individual boluses of etomidate 0.2 mg* kg^{-1} *on CPP in groups A (CFM < 5 μV) and B (CFM > 5 μV). Absolute numbers (percentage of total in group)*

	Group A (CFM < 5 μV)	Group B (CFM > 5 μV)
Decrease in CPP	20 (69%)	36 (37%)
CPP unchanged	4 (14%)	3 (3%)
Increase in CPP	5 (17%)	56 (59%)

the maximum increase being 21 mm Hg. The maximum decrease in CPP was similar in both groups (group A = −28 mm Hg, group B = −25 mm Hg).

There was a strong positive correlation between the decrease in ICP and the decrease in MAP in group A ($r = 0.70$; $P < 0.01$), whereas there was no such correlation in group B ($r = 0.05$) (fig. 2).

Finally, when both groups were combined, there was a positive correlation between the value of the baseline of the CFM trace before the bolus and the subsequent change in CPP ($r = 0.304$; $P < 0.001$), a relationship which was absent when groups A and B were analysed separately.

DISCUSSION

The extent and direction of the change in CPP following the bolus administration of an i.v. anaesthetic agent to a patient with intracranial hypertension will depend on the relative magnitude of the alterations in MAP and ICP.

The change in arterial pressure will be influenced by the anaesthetic agent used (etomidate, for example, causes little cardiovascular depression (Gooding and Corssen, 1977)) and the state of the cardiovascular system before the bolus is administered. In particular, a compensated reduction in circulating volume may be unmasked by i.v. anaesthetics, leading to marked hypotension (Traeger et al., 1983).

The decrease in ICP following the administration of these agents is secondary to a reduction in cerebral blood flow (CBF) and intracranial blood volume (IBV) (Pickerodt et al., 1972; Turner et al., 1973). Thus, the magnitude of the pressure change will depend on the extent of the volume change as well as the intracranial compliance.

Two mechanisms may account for the decrease in CBF and IBV following the administration of an i.v. anaesthetic agent. First, because autoregulation of CBF is often impaired in traumatic coma (Overgaard and Tweed, 1974), decreases in MAP will be associated with passive reductions in CBF. Second, the cerebral metabolic depression produced by these agents will result in a secondary reduction in CBF. Thus, once cerebral metabolism is substantially depressed, further administration of an i.v. anaesthetic agent is unlikely to decrease ICP significantly, except as a passive response to the decreases in MAP. Under these circumstances CPP is unlikely to increase and will often decrease.

In 1974, Michenfelder demonstrated that, in dogs, a continuous high-dose infusion of thiopentone produced a progressive decrease in $CMRo_2$ until cortical electrical activity had been

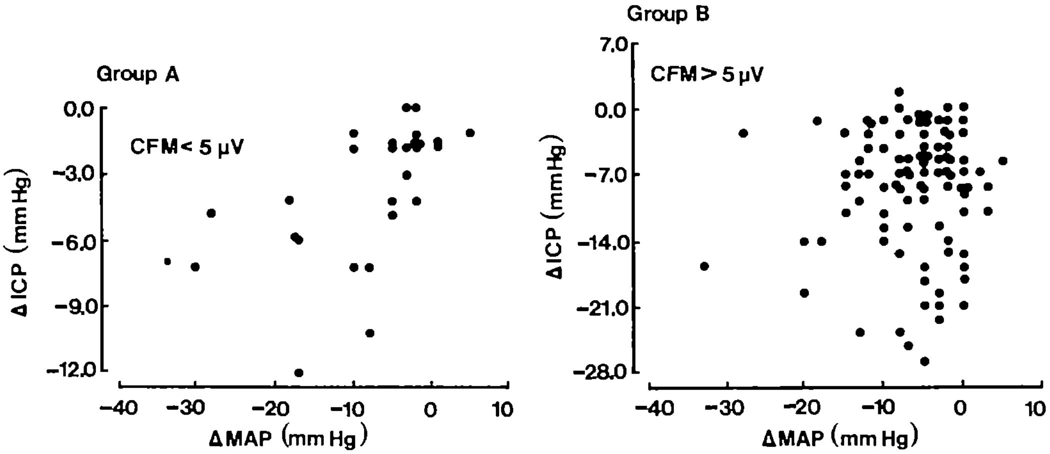

FIG. 2. Scatter diagram of change in ICP against change in MAP following bolus doses of etomidate 0.2 mg kg^{-1} in groups A (CFM < 5 μV) and B (CFM > 5 μV). There is a significant correlation between these two variables in group A ($r = 0.70$; $P < 0.01$), but none in group B ($r = 0.05$; ns).

absolished. Thereafter, additional, larger doses of thiopentone produced no further reduction in $CMRo_2$ (Michenfelder, 1974). Kassell and his colleagues performed similar work in canine models, but also measured CBF. They found that neither $CMRo_2$ nor CBF could be decreased further once sufficient anaesthetic had been given to produce burst suppression of between 30 and 60 s duration on the EEG (Kassell et al., 1980). Thus the degree of suppression of cortical electrical activity indicates the extent of cerebral metabolic depression and it is unlikely that the administration of i.v. anaesthetic agents in the presence of such electrical depression would result in useful reductions in ICP (decreases in ICP unrelated to reductions in MAP, and therefore associated with increases in CPP). The results of this study support this contention.

We have used the CFM rather than the conventional EEG because it is better suited to continuous monitoring in the intensive care unit, interpretation is relatively simple and it is particularly valuable for the detection of cerebral ischaemia (Matoušek et al., 1984). Previous work has shown that when the minimum voltage of the CFM decreases to less than 5 μV there is profound cerebral electrical depression, often equivalent to a "burst suppression" pattern on the conventional EEG (Prior, Maynard and Brierley, 1978). Before analysis of the data, we selected this voltage to discriminate between the two groups. During the period of sedation we were unable to exclude the possibility that, in some instances, this depression might have been a result of cerebral damage rather than the administration of anaesthetic agents.

In the presence of such cerebral electrical depression, the administration of etomidate did produce a small mean decrease in ICP (−3.8 mm Hg), but this was significantly less than that occurring when the CFM was not depressed (−8.6 mm Hg). Since, in addition, MAP often decreased, CPP was usually decreased (in 69% of instances). Furthermore, although CPP increased on 17% of occasions in group A, the magnitude of the increases was usually small (< 2 mm Hg). In only one instance did CPP increase by more than this, and on this occasion a 6-mm Hg increase was principally mediated by an unexplained 5-mm Hg increase in MAP. Finally, the strong correlation between the changes in MAP and ICP in this group suggests that any reduction in ICP which did occur was a passive response to the decrease in MAP.

However, when cerebral electrical activity was not depressed, boluses of etomidate produced larger decreases in ICP (mean −8.6 mm Hg) so that, although a similar degree of hypotension occurred, CPP increased in more than one-half (59%) of instances and overall by a mean of +2.2 mm Hg. In these circumstances, 30% of the boluses produced increases in CPP greater than 6 mm Hg (the maximum increase in group A). Furthermore, in this group there was no correlation between the changes in MAP and ICP; this suggests that hypotension was not the sole mechanism responsible for the decrease in ICP. Although CBF was not measured in this study, it is probable that, when the CFM was not suppressed, the decreases in ICP were largely in response to a reduction in CBF caused by depression of cerebral metabolic rate.

The positive correlation (in the combined data) between the value of the baseline of the CFM and the subsequent change in CPP provides further support for the hypothesis that the effect of the boluses of etomidate on CPP is influenced by the preceding cerebral electrical activity.

In conclusion, the CFM would seem to be a clinically useful guide to the administration of etomidate (and probably other anaesthetic agents (Procaccio, personal communication)), to patients in traumatic coma with intracranial hypertension. In our patients, administration of etomidate in the presence of a minimum CFM voltage of less than 5 μV produced relatively small reductions in ICP and no useful increase in CPP; indeed CPP was usually reduced. Under these circumstances, further administration of i.v. anaesthetic agents is unlikely to be of benefit and should probably be avoided. In the absence of such depression, CPP increased following more than one-half the boluses. However, marked hypotension sometimes resulted in potentially damaging decreases in CPP, even in this group. We would recommend that i.v. boluses of anaesthetic agents should be administered to patients in traumatic coma only when the CFM voltage is greater than 5 μV, the cardiovascular system is stable and the circulating volume adequate. Furthermore, since a positive correlation between the initial ICP and the extent of the subsequent decrease has been demonstrated previously (Turner et al., 1973; Prior et al., 1983), such treatment should be restricted to those with significant intracranial hypertension (for example, > 25 mm Hg).

APPENDIX

MEASUREMENTS TAKEN FROM CHART RECORDS

Variable	Unit
Etomidate infusion rate	$\mu g\ kg^{-1}\ min^{-1}$
Etomidate dose	mg
Procedure or stimulus (if any associated with bolus)	—
Systolic and diastolic arterial pressures before bolus; steady state	mm Hg
Systolic and diastolic ICP before bolus; steady state	mm Hg
Maximum and minimum CFM before bolus; steady state	µV
Systolic and diastolic arterial pressures after bolus; maximum change	mm Hg
Systolic and diastolic ICP after bolus; maximum change	mm Hg
Maximum and minimum CFM after bolus; maximum change	mms

Derivation of calculated values

$$\text{Mean ICP (ICP)} = \frac{\text{Systolic ICP} - \text{Diastolic ICP}}{2}$$

$$\text{Mean arterial pressure (MAP)} = \text{Diastolic AP} + \frac{\text{pulse pressure}}{3}$$

$$\text{CPP} = \text{MAP} - \text{ICP}$$

Change in ICP (ICP) = ICP after bolus − ICP before bolus
Change in CPP (CPP) = CPP after bolus − CPP before bolus

Central venous pressure (measured at mid-axillary line) was never sufficiently increased in these patients (all of whom were nursed in a 45° semi-reclining posture) to influence CPP and was therefore not included in the calculation.

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DEPRESSION OF CORTICAL SOMATOSENSORY EVOKED POTENTIALS BY NITROUS OXIDE

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Sensory evoked potentials are used in some centres to monitor patients whose major nerve tracts are at risk during surgery. Such monitoring may be valuable during central nervous system surgery or the operative correction of scoliosis. Many of these operations are conducted with a narcotic-based anaesthetic, which includes the use of nitrous oxide. Nitrous oxide depresses midbrain and cerebral evoked responses to dental pulp stimulation (Haugen and Melzack, 1957; Benedetti et al., 1982) and cortical responses to auditory stimulation (Lader and Norris, 1968, 1969; Fenwick et al., 1979; Harkins et al., 1982). It is possible that the effects of nitrous oxide and narcotics combine to decrease the somatosensory evoked responses (SSEP).

This study measured SSEP during skin closure, when nitrous oxide was added to the inhaled gases of patients undergoing central nervous system or spinal surgery under a narcotic-based anaesthetic.

SUMMARY

The effects of the inhalation of 50% nitrous oxide on somatosensory evoked potentials during a fentanyl–oxygen anaesthetic technique for central nervous system surgery were evaluated. The latency and amplitude of the first cortical wave were obtained using conventional somatosensory techniques with median or posterior tibial nerve stimulation. Data were collected before and after the inhalation of 50% nitrous oxide in oxygen introduced at the conclusion of the surgical procedure. The addition of nitrous oxide was associated with consistent decreases in the amplitude of somatosensory evoked potentials, but with no significant changes in latency. Since no electrical, physiological, or surgical event was associated with these changes, the results suggest that they were attributable to nitrous oxide per se.

PATIENTS AND METHODS

Intraoperative SSEP monitoring was used in the care of 90 consecutive patients (ASA class II–III) during spinal cord, posterior fossa, or supratentorial surgical procedures. The records of these patients were evaluated and 44 were chosen for study by the exclusion of those in whom nitrous oxide was not used, or in whom other factors could have altered the SSEP (technical problems were encountered, there were changes in ventilation, temperature or arterial pressure, or other anaesthetics were administered). The study was conducted with approval from the Northwestern Memorial Hospital Institutional Review Board.

Patients and anaesthesia

All patients were anaesthetized similarly, using a narcotic-based, relaxant technique. Premedication was with atropine or hyoscine 0.4 mg i.m. sometimes supplemented with morphine 0.05–0.15 mg kg^{-1} by mouth 45–60 min before surgery. After pretreatment with pancuronium 0.02 mg kg^{-1}, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and a loading dose of fentanyl 10–20 μg kg^{-1}. Sterile subdermal needle electrodes were inserted over the posterior tibial nerve (PTN) at the ankle, or the median nerve (MN) at the wrist and the constant current necessary to produce a motor response established

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(motor threshold). Additional pancuronium (to a total of 0.1 mg kg^{-1}) was given and the trachea intubated. The patients were ventilated with 100% oxygen in a low flow (0.7–1.0 litre min^{-1}) semi-closed circle system. Additional fentanyl (to a total of 20–50 μg kg^{-1}) and pancuronium were administered as required. Usually, an inhalation agent (halothane, enflurane or isoflurane) was administered at an inspired concentration of 0.25 MAC during surgical manipulation. Nitrous oxide, at an inspired concentration of 50%, was commenced during skin closure and at least 30 min after cessation of the inhalation agent. The fresh gas flow rate was increased to 2–4 litre min^{-1}. The SSEP chosen for analysis were recorded before the introduction of nitrous oxide and after the establishment of a new steady state during the 7–10th min of exposure to 50% nitrous oxide. Neither deep body temperature nor end-tidal carbon dioxide concentration altered during the study period.

Recording of evoked potentials

Stimulation of the median or posterior tibial nerves was with a 300-ms square wave at 5.4 Hz using a constant current at least 2 mA above the predetermined motor threshold. The cortical evoked potentials were recorded using sterile subdermal needle electrodes. The active recording electrode was placed over the contralateral hand area (2 cm posterior to C_3 or C_4 of the international 10–20 system) or foot area (midline 2 cm posterior to C_z) for MN and PTN, respectively. Both types used a reference subdermal electrode placed in the midline on the forehead (F_z) and a silver–silver chloride ground electrode on the shoulder. The resulting electrical response from 250–500 stimulations for 50 ms (MN) or 100 ms (PTN) following the stimulus were amplified, filtered and digitized using a Nicolet CA 1000 signal averager. Bandpass filtration was set between 5 and 1500 Hz (PTN) or 5 and 3000 Hz (MN). Data were plotted so that a relative positivity at the active electrode caused an upward deflection.

The latency of the major cortical peak (recorded as negativities at about 25 ms for MN and 45 ms for PTN) was derived as the time (ms) from stimulus to maximal amplitude of the peak. Peak amplitude was measured as the difference (μV) between this peak and the preceding peak of opposite polarity. The latency and amplitude information were determined once the peaks were stable before and after nitrous oxide administration. The data were analysed using least squares linear regression. The null hypothesis was rejected when $P < 0.05$ using the paired *t* test.

RESULTS

Nitrous oxide produced a consistent decrease in the amplitude of the cortical SSEP. Figure 1 shows serial recordings taken from single limb stimulation of the posterior tibial nerve. In this patient, as in the others, nitrous oxide produced a marked decrease in amplitude of the SSEP recording, which recovered with discontinuation of the nitrous oxide. Except for transient alterations in latency during skin closure, the latency of the negative peak remained essentially unchanged.

The steady state cortical amplitudes before and

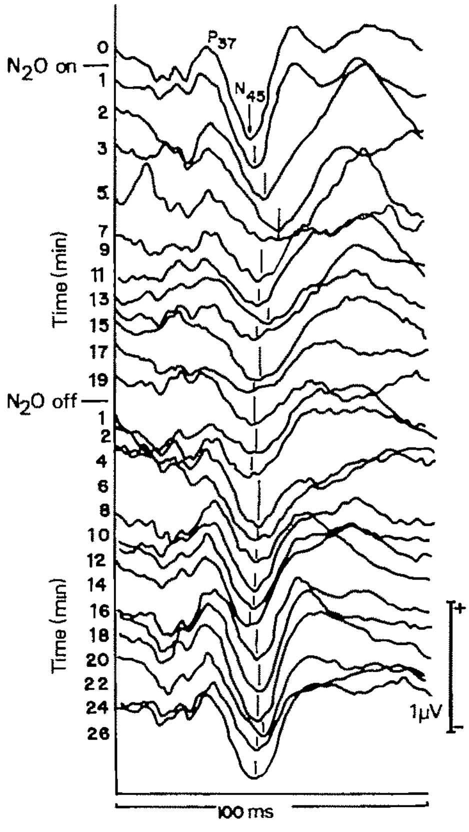

FIG. 1. Serial cortical recordings of posterior tibial nerve somatosensory evoked potentials during the introduction and withdrawal of nitrous oxide during closure after spinal cord tumour biopsy. The waves are plotted so that a relative positivity at C_z' is plotted upward. The peak of interest for this study at about 45 ms is indicated (N_{45}).

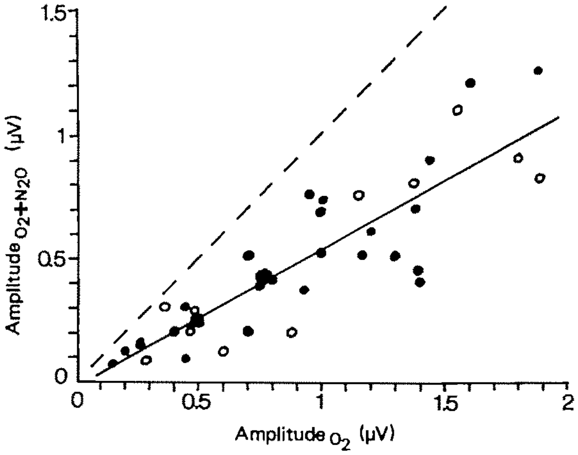

FIG. 2. Plot of SSEP steady-state cortical amplitudes during 100% oxygen administration and after inhalation of 50% oxygen with 50% nitrous oxide. Median nerve data are shown in open circles and posterior tibial nerve values are shown in closed circles. —— = Least squares regression for the combined data; ---- = line of identity.

after the inhalation of nitrous oxide in all 44 patients are shown in figure 2. Using data for all the patients, linear regression analysis (table I) gave the equation $y = 0.56x - 0.04$ ($r = 0.88$) where y is the amplitude of the SSEP after inhalation of nitrous oxide and x represents the amplitude before the inhalation. Comparison of values before and after nitrous oxide using the paired t test revealed a significant decrease in amplitude ($P < 0.01$).

Latencies before nitrous oxide were 45.9 ms ± 2.7 ms (SD) (PTN, range 41.0–49.5) and 22.3 ms ± 2.0 ms (SD) (MN, range 20.0–26.2). During nitrous oxide administration latency increased in 17 patients, decreased in 18 and was unchanged in nine. There was no statistically significant difference in latency before and after the administration of nitrous oxide.

TABLE I. *Regression line calculated from the steady state amplitudes (μV) before (x) and after (y) the inhalation of 50% nitrous oxide in oxygen*

Modality	Regression line	Correlation coefficient
Median nerve ($n = 12$)	$y = -0.04 + 0.57x$	0.86
Posterior tibial nerve ($n = 32$)	$y = -0.04 + 0.55x$	0.91
Combined	$y = -0.04 + 0.56x$	0.88

DISCUSSION

A significant decrease in the amplitude of SSEP occurred when 50% nitrous oxide was administered during a narcotic–oxygen–relaxant-based anaesthetic for surgery of the central nervous system. The steady response data (fig. 2) suggest that 50% nitrous oxide decreased the amplitude of the measured waves by approximately half, whatever the control voltage. If other known causes of changes in evoked potential occurred during the study period, data from that patient were excluded. Thus end-tidal carbon dioxide concentration, rectal temperature and arterial pressure were unchanged. No narcotic had been administered in the previous hour and volatile inhalation agents had been discontinued for at least 30 min. The concentration of these agents would be expected to be declining slowly and to be associated with a slow increase in amplitude rather than the decrease seen coincident with the administration of nitrous oxide. Other causes of alteration include the effects of surgical stimulation. Skin closure has not been reported to cause a decrease in amplitude and it is unlikely that such an acute deterioration would occur as a consequence of surgical manipulation. Thus the change seen in this study coincident with the administration of nitrous oxide is unlikely to be the result of physiological, other anaesthetic or surgical factors.

These results are similar to those of studies which examined the effect of the inhalation of nitrous oxide on cortical evoked responses and demonstrated a dose-related, linear decrease in amplitude. Lader and Norris (1968, 1969) found nitrous oxide-related decreases in amplitude of cortically (50–130 ms) derived evoked potentials from auditory responses. Jarvis and Lader (1971) and Fenwick and colleagues (1979) found similar decreases in the amplitudes of cortical responses (100–300 ms) attributable to nitrous oxide. Other studies using electrical stimulation of the dental pulp and recording of cortical responses (100–250 ms) also showed a reduction in amplitude. As in this study, previous studies (Fenwick et al., 1979; Benedetti et al., 1982), have demonstrated a reduction in amplitude of approximately 50% when concentrations of nitrous oxide approached 50%.

These data suggest that nitrous oxide and narcotics are additive in depressing intraoperative SSEP during nitrous oxide–narcotic–relaxant anaesthesia. In this study, acute alterations in the nitrous oxide concentration in the absence of major changes in the narcotic delivery altered the SSEP. Previous studies have indicated that the effect of nitrous oxide is dose related. Pathak, Brown and Cascorbi (1982) and Pathak and others (1983) have shown that SSEP amplitudes varied coincidentally with the bolus administration of narcotics during a nitrous oxide–narcotic anaesthetic when the inspired concentration of nitrous oxide was held constant. This suggests that the maintenance of constant inspired concentrations of nitrous oxide as well as of narcotic concentration may be necessary to minimize changes in SSEP amplitude during a nitrous oxide–narcotic anaesthetic.

This decrease in amplitude results in a deterioration in signal quality and may produce an unmeasurable signal in patients with very small signals. This may prevent monitoring or reduce its usefulness by requiring more extensive signal acquisition methods (e.g. a longer period of signal averaging). The use of a narcotic–oxygen anaesthetic may, therefore, be valuable in patients with very small signals where the attenuation resulting from nitrous oxide is unacceptable.

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EFFECTS OF ANAESTHETIC TECHNIQUE ON DEEP VEIN THROMBOSIS

A Comparison of Subarachnoid and General Anaesthesia

P. J. McKENZIE, H. Y. WISHART, I. GRAY AND G. SMITH

SUMMARY

Forty patients with fractured neck of femur were allocated randomly to undergo surgery under general anaesthesia (GA) or subarachnoid anaesthesia (SAB). After operation, the incidence of deep vein thrombosis (DVT), assessed by venography, was found to be 40% in the SAB group, which was significantly lower than the incidence (76.2%) in the GA group. These observations may account for the previously reported effect of SAB, in comparison with GA, in reducing early postoperative mortality in this category of patient.

It has been known for many years that patients with a fractured neck of femur have a high incidence of deep vein thrombosis (DVT) (Sevitt and Gallagher, 1961; Field, Kakkar and Nicolaides, 1972; Moskovitz et al., 1978; Xabegras, Gray and Ham, 1978). Recently, interest has focused on the effect of different techniques of anaesthesia on the incidence of postoperative DVT following surgical repair of fractured neck of femur.

Although, in elective hip replacement the use of subarachnoid in comparison with general anaesthesia was associated with reduced postoperative frequency of DVT (Thorburn, Louden and Vallance, 1980), the effect of spinal (subarachnoid) anaesthesia on DVT following repair of fractured neck of femur is unclear. Davis, Quince and Laurenson (1980) found a reduced incidence of DVT with subarachnoid spinal anaesthesia for this condition, but their study utilized the fibrinogen uptake test, a method which is inappropriate and inaccurate in this situation (Field, Kakkar and Nicolaides, 1972; Morris and Mitchell, 1977; Browse, 1978; Louden et al., 1978).

Despite the identical long term outcome after repair of fractured neck of femur following both subarachnoid and general anaesthesia (McKenzie, Wishart and Smith, 1984), early postoperative mortality is reduced by the former technique (McLaren, Stockwell and Reid, 1978; McKenzie, Wishart and Smith, 1984) and it has been postulated that the difference in mortality may be related to alteration in the incidence of postoperative deep vein thrombosis and subsequent pulmonary embolism. The present study was undertaken to examine this hypothesis, using ascending venography in patients after repair of fractured neck of femur undertaken under either subarachnoid block or general anaesthesia.

PATIENTS AND METHODS

Forty patients admitted for "pin and plate" repair of fractured neck of femur were allocated randomly to receive subarachnoid blockade (SAB group; 20 patients, 16 female) or general anaesthesia (GA group; 20 patients, 14 female). They received fluids i.v. for at least 12 h before surgery to minimize any pre-existing dehydration. No formal premedication was given, but analgesic drugs were administered if required.

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TABLE I. *General features of patients included in the study, expressed as mean ± SEM. Ranges in parentheses. ns = Not significant*

	GA group	(Range)	SAB group	(Range)	Significance
Age (yr)	72.3 ± 2.8	(33–87)	73.9 ± 4.1	(19–94)	ns
Admission-to-surgery interval (day)	1.8 ± 0.16	(1–3)	2.0 ± 0.18	(1–4)	ns
Preoperative serum urea (mmol litre^{-1})	6.1 ± 0.6	(1.5–10.6)	8.4 ± 1.2	(2.4–22.1)	ns
Estimated blood loss (ml)	243 ± 47	(85–990)	348 ± 64	(60–1200)	ns
Fluid infused during surgery (ml)	923 ± 68	(300–1500)	1300 ± 94	(700–2200)	$P < 0.05$
Duration of surgery (min)	79 ± 4.1	(60–130)	93.5 ± 5.6	(60–150)	$P < 0.05$

Anaesthesia

General anaesthesia. General anaesthesia was induced with Althesin (Glaxo) 1–3 ml i.v. Following the administration of suxamethonium 50 mg, the trachea was intubated with a cuffed endotracheal tube and anaesthesia was maintained with 66% nitrous oxide and 0.75–1.25% halothane in oxygen. The patients breathed spontaneously via a semi-closed breathing system with carbon dioxide absorption, with a fresh gas flow of 3 litre min^{-1}.

Spinal anaesthesia. Hyperbaric cinchocaine 1.2–1.5 ml ("heavy Nupercaine") was injected slowly (without barbotage) to the subarachnoid space at the L3–4 or L4–5 space via a 22-gauge "spinal" needle. The block was performed with the patient in the horizontal lateral position with the fractured hip dependent. Discomfort caused by turning the patient to this position was transient and minimized by gentle handling. Two minutes after injection, the patient was turned to the supine position and maintained horizontal to produce a bilateral block. Small doses of diazepam were administered i.v. if sedation was necessary.

Venography

Venography was performed as described by Louden and others (1978), 7–10 days after operation. In one patient, examination was undertaken on the 4th day.

RESULTS

There were no significant differences in mean age (Student's *t* test) or sex distribution (Fisher's test).

There were no significant differences between groups in preoperative serum urea concentrations, interval between admission and surgery, or estimated blood loss (table I). However, the mean duration of surgery was significantly longer in the SAB group (93.5 min) than in the GA group (79 min) ($P < 0.05$). The mean volume of fluid infused was also significantly greater in the SAB group (1300 ml) than in the GA group (923 ml) ($P < 0.05$) (table I).

The incidence of DVT in the SAB group (40%) was significantly lower than in the GA group (75%) by Fisher's test ($P < 0.05$). Ten per cent of patients in the SAB group had unilateral DVT in the leg opposite to that with the fracture. Forty-five per cent of patients in the GA group and 15% in the SAB group had unilateral DVT on the same side as the fracture. Bilateral DVT occurred in eight of the 16 patients with DVT in the GA group and three of eight with DVT in the SAB group. Clinical evidence of DVT was noted in only three patients, all in the SAB group (table II).

There was no discernible difference between the two groups in the pattern of distribution of thromboses, which occurred at multiple sites in many patients (table III).

There was no significant difference in outcome

TABLE II. *Number of patients (%) in each group with venographic evidence of DVT.* **P* <0.05

	GA group ($n = 20$)	SAB group ($n = 20$)
DVT present	16 (75%)*	8 (40%)
Bilateral DVT	8 (40%)	3 (15%)
Unilateral		
Operated side	9 (45%)	3 (15%)
Non-operated side	0	2 (10%)
Clinically evident	0	3 (15%)

TABLE III. *Site of DVT as demonstrated by venography. Note that many patients had multiple thromboses*

	GA group		SAB group	
Sites of DVT	Operated side	Non-operated side	Operated side	Non-operated side
Iliac	3	1	0	1
Femoral	10	2	5	2
Popliteal	3	1	3	2
Calf	9	7	5	4

between the two groups in the year following operation (table IV). Only two patients died within 28 days of operation, both in the GA group (on the 4th and 9th days) and both had DVT. The patient who died on the 4th day had, coincidentally, undergone venography earlier in the day and it was concluded that death resulted from cerebrovascular accident.

DISCUSSION

This study in patients with fractured neck of femur has demonstrated that, in comparison with general anaesthesia, the use of SAB was accompanied by a significantly lower incidence of postoperative DVT. It is important to note that, in assessing the incidence of DVT, our study utilized venography — a technique which is considered to be the most accurate method available for the detection of this condition (Browse, 1978). Various other studies have used the fibrinogen uptake test, which is very inaccurate after hip surgery, with a false positive rate of approximately 30% (Louden et al., 1978) and a false negative rate of between approximately 8% (Field, Kakkar and Nicolaides, 1972) and 18% (Morris and Mitchell, 1977). It is also of little value in the detection of thrombi above the knee (Morris and Mitchell, 1977). Although Davis, Quince and Laurenson (1980) found a lower incidence of DVT (46%) after subarachnoid anaesthesia than after general anaesthesia (76%) in groups of patients similar to those in the present study, they used the less reliable fibrinogen uptake test.

TABLE IV. *Fate of patients 1 yr after surgery*

	GA group ($n = 20$)	SAB group ($n = 20$)
Hospital deaths	4	3
Returned home	13	14
Died at home	1	0
Remained in hospital	1	2
Psychogeriatric care	1	1
Community care	1	0

A similar association between SAB and reduced incidence of DVT (assessed by venography) has been reported previously in patients undergoing elective hip replacement (Thorburn, Louden and Vallance, 1980). The use of spinal blockade produced by extradural anaesthesia (as opposed to subarachnoid blockade) was also shown recently to be associated with a reduced incidence of DVT, compared with general anaesthesia, in patients undergoing elective hip replacement (Modig, Borg, Karlstrom et al., 1983). Furthermore, Modig's group demonstrated that there was a high incidence of abnormalities of lung perfusion scans in the GA (33%) in comparison with the extradural group (10%), suggesting a significant difference in the incidence of pulmonary embolism.

Studies comparing the incidence of DVT following thoracic extradural or general anaesthesia in abdominal surgery have failed to reveal significant differences. With abdominal surgery requiring thoracic extradural analgesia, alone (Hendolin, Tuppurainen and Lahtinen, 1982) or in combination with general anaesthesia (Hendolin, Tuppurainen and Lahtinen, 1982; Mellbring et al., 1983), no effect was found on the incidence of DVT. In patients undergoing open prostatectomy, Hendolin, Mattila and Poikolainen (1981) demonstrated a significant difference in postoperative DVT detected by fibrinogen uptake in a GA group (52%) in comparison with an extradural group (12%), but this was not confirmed by venography.

There are two main mechanisms whereby spinal anaesthesia might cause reduction in the frequency of postoperative deep vein thrombosis: first, by improvement in blood flow in the lower limbs as a result of reduction in vascular resistance in the area below the block, or changes in blood viscosity resulting in maintenance of, or increase in, flow in comparison with a reduction achieved by general anaesthetic techniques; and second, by a decrease in the ability of the blood to coagulate.

There is some evidence that spinal anaesthesia, compared with general anaesthesia, may result in increased blood flow in limbs, and induction of general anaesthesia is known to reduce lower limb blood flow substantially (Clark and Cotton, 1968; Kemble, 1971; Poikolainen and Hendolin, 1983). Modig, Malmberg and Karlstrom (1980) demonstrated an increase in arterial inflow, venous emptying rate and venous capacity after the institution of extradural block in patients undergoing hip replacement. In addition, spinal anaesthesia (SAB) has been demonstrated to be associated with a significant reduction in blood viscosity in patients with hip fracture (Drummond, et al., 1980), partly as a result of haemodilution, but also because of an increase in red cell deformability; in contrast, general anaesthesia was shown to produce a decrease in red cell deformability which could be reproduced by exposure to halothane *in vitro*.

There is also some evidence that spinal anaesthesia might be associated with decreased blood coagulability in comparison with general anaesthesia. Postoperative fibrinolytic activity is decreased less after extradural anaesthesia than after general anaesthesia (Modig, Borg, Bagge et al., 1983) and Simpson and colleagues (1982) found enhancement of fibrinolysis when extradural block was combined with light anaesthesia in patients undergoing hysterectomy. In addition, Zahavi, Price and Kakkar (1980) found enhanced platelet activation and release associated with halothane anaesthesia. However, it is conceivable that extradural anaesthesia may have effects on blood coagulability different than those of subarachnoid anaesthesia as a result of the larger volumes of local anaesthetic solution utilized in the former technique; local anaesthetic agents are known to inhibit platelet adhesion (O'Brian, 1961), platelet aggregation and release (Feinstein, Fiekers and Fraser, 1976; Cazenave, Benveniste and Mustard, 1979) and leucocyte migration and aggregation (Giddon and Lindhe, 1972). Lignocaine, given as an i.v. infusion during operation and for the first 6 days after operation, reduced significantly the incidence of DVT in patients undergoing hip replacement in a comparison with a control group given 5% dextrose (Cooke et al, 1977).

In conclusion, this study is the first to demonstrate convincingly that, compared with general anaesthesia, the use of subarachnoid blockade is associated with a reduction in the incidence of DVT in patients undergoing repair of fractured neck of femur. Thus it complements previous studies demonstrating a similar association for extradural anaesthesia and also for SAB in patients undergoing elective total hip replacement. The relatively small sample size of the present study (dictated by the high expense and logistic requirements of venography) may account for our failure to observe a difference in mortality rates between the SAB and GA groups which could be related to the incidence of DVT. A reduced incidence of DVT may nevertheless be postulated as a possible mechanism for the improved mortality rate seen by McLaren, Stockwell and Reid (1978) and McKenzie, Wishart and Smith (1984) in the early postoperative period following surgery on fractured neck of femur under subarachnoid anaesthesia, compared with general anaesthesia.

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MORPHINE SULPHATE SLOW RELEASE
Comparison with i.m. Morphine for Postoperative Analgesia

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SUMMARY

Eighty patients undergoing abdominal surgery were studied after operation. Morphine was administered regularly every 4 h by either the i.m. (morphine sulphate 10 mg) or the oral route (MST Continus 20 mg) in a double-blind double-dummy trial. Both MST and i.m. morphine provided satisfactory postoperative analgesia, but significantly greater amounts of supplementary i.m. morphine were required in the MST group. More adverse effects were reported by the patients in the i.m. morphine group. The mean serum morphine concentration in 12 patients in the MST group was 1.7 ng ml^{-1} at 08.00 h and 19.5 ng ml^{-1} at 16.00 h on the 1st day after operation, suggesting impaired gastric emptying in the early postoperative period. It is therefore recommended that further studies of the bioavailability of MST in the early postoperative period be undertaken before any recommendations are made regarding its routine use for pain relief at that time.

There has been increasing interest in recent years in the administration of opioids by non-parenteral routes in the treatment of postoperative pain (Ellis et al., 1982; Fell, Chmielewski and Smith, 1982; Derbyshire et al., 1984; Hanning et al., 1984). Previous studies from this department have demonstrated that acceptable postoperative analgesia can be achieved by the administration of slow release morphine sulphate tablets (MST) at approximately 6-hourly intervals. Such treatment has been compared with conventional intermittent i.m. morphine (Fell, Chmielewski and Smith, 1982) and with 6-hourly sublingual buprenorphine (Derbyshire et al., 1984). To date, however, oral MST and morphine i.m. have not been compared in a double-blind, double-dummy investigation.

The present study was designed to provide further information on the use of MST for postoperative analgesia. There were several objectives. First, comparison of MST with morphine 4-hourly i.m. provides a more stringent comparison of the efficacy of MST than was undertaken in previous studies. Second, since a single dose of MST releases morphine over at least a 7-h period (Vater et al., 1984), there is a potential risk of cumulation with 4- or 6-hourly dose regimens. In order to examine this particular question, blood was sampled at the beginning and end of the assessment period for measurement of serum morphine concentrations. Third, since previous studies of MST assessed analgesia only at 24 and 48 h after surgery, an opportunity was taken to assess analgesia in the early postoperative period.

PATIENTS AND METHODS

Eighty patients about to undergo cholecystectomy, hysterectomy or herniorrhaphy gave informed consent to participate in this study which had been approved by the District Ethical Committee. All patients were within the age range 18–65 yr and only those without significant respiratory or cardiovascular dysfunction were included in the study. No patient was receiving opioids at the time of admission to hospital.

Patients were allocated randomly to receive postoperative analgesia with either i.m. (morphine sulphate, Evans Medical Limited) or oral (MST Continus, Napp Laboratories) morphine sulphate. Matched dummies of either wax matrices (for the i.m. morphine group) or 5% dextrose ampoules

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(for the oral morphine group) were packed with the appropriate active drug in coded boxes labelled for each patient. The nurses administering the morphine and the observers were unaware of the route of administration of active drug until the end of the study.

Anaesthesia. Patients were premedicated with diazepam 10 mg by mouth 1–2 h before surgery. Anaesthesia was induced with thiopentone and maintained with 66% nitrous oxide in oxygen, supplemented by either morphine (up to 10 mg) or papaveretum (up to 20 mg) and a volatile agent (halothane or enflurane), if required. Morphine sulphate was given i.v. to any patient complaining of pain in the recovery room before transfer to the ward. This dose was not included in the calculation of the amount of postoperative analgesic administered.

Upon return to the ward, patients received tablets and an injection every 4 h. The doses (1 ml i.m., 2 tablets orally) were halved or omitted if the nursing staff considered that the patient was oversedated. Supplementary doses (escape doses) of morphine i.m. were available to the patient upon request and recorded.

Assessment. All assessments were undertaken by two observers (A.B. and P.A.P.): the analgesia regimens and procedures were divided evenly between both. Linear analogue scales (LAS—10 cm horizontal lines) were used for the assessment of pain, sedation, nausea and dizziness. Peak expiratory flow rate (PEFR) was measured at each assessment (Wright Peak Flow Gauge). Overall acceptability was assessed by means of a questionnaire (Ellis et al. 1982) (table II). The LAS and use of the Peak Flow Gauge were explained to the patient before surgery and a control PEFR was recorded using the best of three attempts.

At 08.00 h on the 1st day after operation, at 2-hourly intervals thereafter until 18.00 h, patients were asked to rate pain, sedation, nausea and dizziness on the LAS and a PEFR was recorded. At 18.00 h a "Patient Satisfaction" questionnaire was completed. At 09.00–10.00 h on the 2nd day after operation, a final PEFR was measured and the questionnaire completed again.

Serum morphine concentrations were measured in 12 patients (nine hysterectomy, two cholecystectomy, one herniorrhaphy). Blood was sampled at 08.00 h and at 16.00 h (2 h after a regular dose of morphine) on the 1st day after operation. Serum was separated after coagulation and stored at −18 °C until required for measurement of morphine concentrations using high pressure liquid chromatography with electrochemical detection (Aitkenhead et al., 1984).

Analysis of data was undertaken using Student's *t* test, paired or unpaired, as appropriate for data with an expected normal distribution, Wilcoxon Rank Sum test for data from the linear analogue scores, and Chi squared test (with Yates' correction) for other data. $P < 0.05$ was taken as the level of statistical significance.

RESULTS

Data from the three types of operation have been combined, since exclusion of the hernia group ($n = 10$) and separate analysis of the hysterectomy and cholecystectomy groups did not alter the pattern of results. There were no differences between the two groups in respect of age, sex or smoking status. However, the MST group were taller and heavier than the i.m. morphine group (table I).

Mean pain score was greater in the MST group at 08.00 h (fig. 1) and mean nausea score was greater in the i.m. morphine group at 10.00 h (fig. 2), but otherwise there were no significant differences between the groups in respect of pain, nausea, sedation or dizziness. There was a consistent trend for the MST group to exhibit a lower incidence of unwanted effects as shown by the summated side effect scores (fig. 3).

Mean PEFR was 45% of the preoperative control value at the first assessment period. There was an improvement toward the control value

TABLE I. *Demographic data (mean ± SEM).* **$P < 0.05$

	MST ($n = 39$)		Morphine i.m. ($n = 35$)
Age (yr)	43 (1.7)		46 (1.8)
Male/female	7/32		5/30
Height (cm)	166 (1.2)	**	162 (1.1)
Weight (kg)	70 (2.1)	**	63 (1.3)
Smokers	16		13
PEFR (litre min^{-1})	460 (14)		447 (13)
Time to first assessment (h)	19 (0.4)		19 (0.4)
Operation			
Cholecystectomy	14		12
Hysterectomy	20		18
Herniorrhaphy	5		5

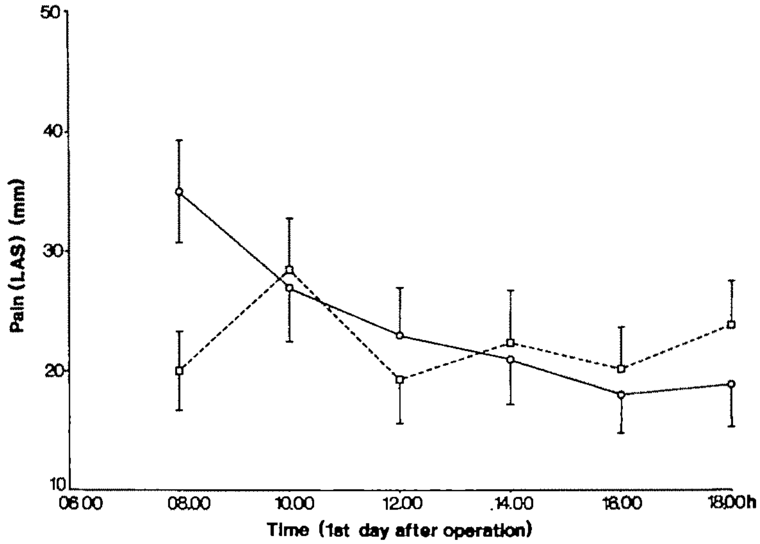

FIG. 1. Linear analogue pain scores (mm) during first day after operation in patients receiving MST (——) or i.m. morphine (---) (mean values). Bars represent SEM.

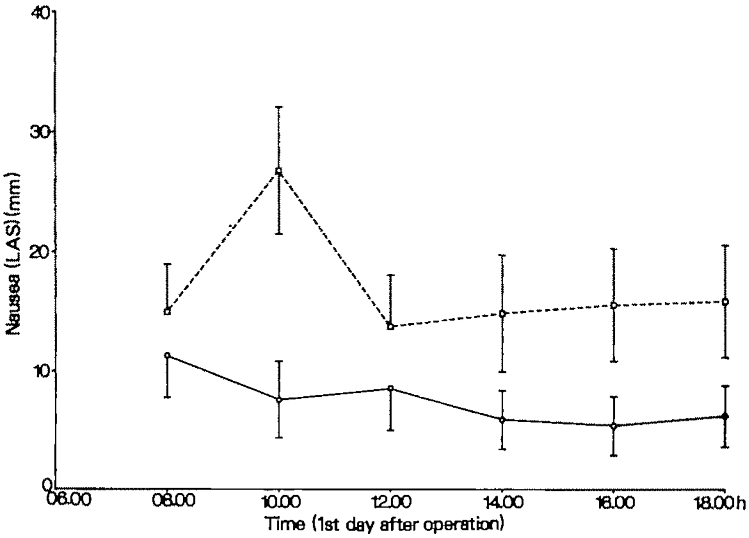

FIG. 2. Linear analogue nausea scores (mm) during first day after operation in patients receiving MST (——) or i.m. morphine (---) (mean values). Bars represent SEM.

during the 1st and 2nd days after operation, but there were no significant differences between groups at any assessment point and therefore data have been pooled to provide figure 4. There was a significant negative correlation between linear analogue pain score and percentage change in PEFR ($r = -0.42$, $P < 0.001$) although there was considerable scatter about the line of best fit (fig. 5).

More supplementary morphine was required in the MST than in the i.m. group (table II). The number of extra doses administered was significantly greater in the group receiving MST; 10 (25%) of the MST group required supplementary analgesia in the first 12 h after operation compared with six in the i.m. morphine group ($P < 0.05$, Chi squared test). Thirteen extra doses of analgesia were administered to the MST group and six to

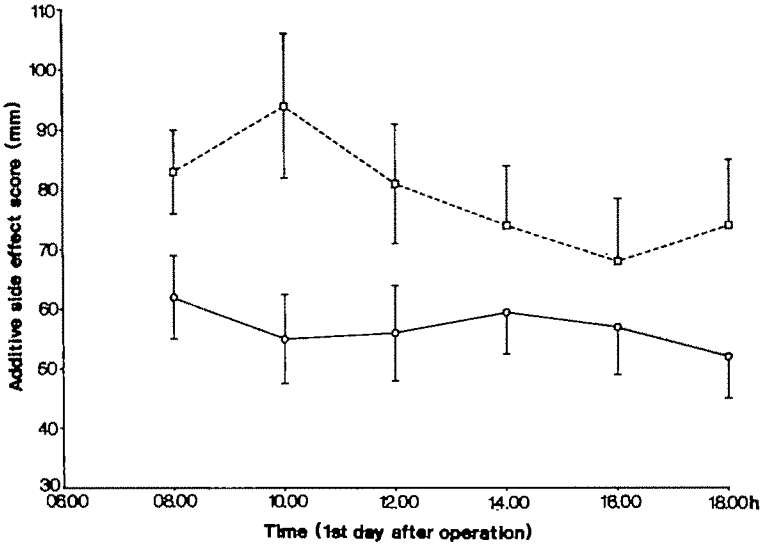

FIG. 3. Additive side effect score (arithmetic sum of linear analogue scores for nausea, sedation and dizziness) (mm) during first day after operation in patients receiving MST (——) or i.m. morphine (---) (mean values). Bars represent SEM.

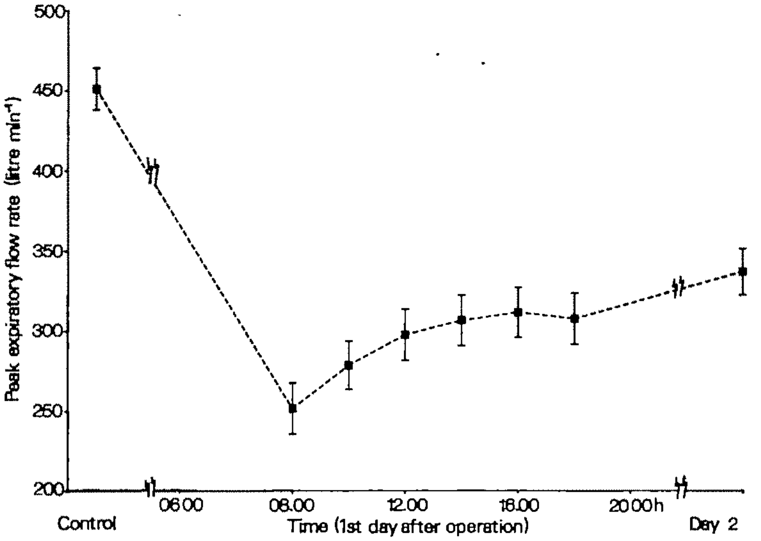

FIG. 4. Peak expiratory flow rate (litre min^{-1}). Control (before operation), 1st and 2nd days after operation in all patients (mean values). Bars represent SEM.

the i.m. morphine group within the first 24 h ($P < 0.05$, Chi squared test). This suggests that the MST group in general received less analgesia than the i.m. group from the regimen under investigation. This is also supported by the observation that the number of times the prescribed dose of morphine and placebo was reduced differed between groups (table II). In the first 12 h nine and 17 patients received reduced doses (MST and i.m. morphine, respectively), whereas in the second 12-h period the numbers were 30 and 37, respectively. When these numbers are combined,

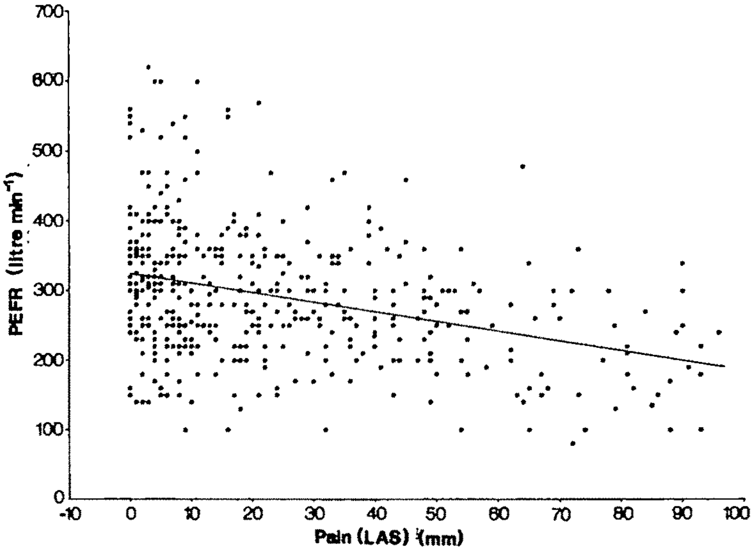

FIG. 5. Scatter diagram: linear analogue pain scores (mm) plotted against peak expiratory flow rate (litre min^{-1}) during 1st day after operation in all patients. Line of best fit derived by analysis of least squares ($r = -0.42$, $P = < 0.001$).

TABLE II. *Postoperative data (mean ± SEM).* ** *P < 0.05 for 24-h combined data*

	MST ($n = 39$)		Morphine i.m. ($n = 35$)
Mean additional dose of morphine (mg)	4.1 (1.1)	ns	1.7 (0.6)
Total No. additional doses of morphine			
First 12 h	10	**	6
Second 12 h	3		0
Total No. reduced doses of morphine			
First 12 h	9	**	17
Second 12 h	30		37
Mean dose of anti-emetic administered: prochlorperazine (mg)	24.5 (3.7)	ns	24.1 (3.2)

TABLE III. *Patient Satisfaction Questionnaire (number of affirmative answers)*

	MST ($n = 39$)		Morphine i.m. ($n = 35$)
Postop. pain < expected?	19	ns	22
Analgesia acceptable?	37	ns	33
Troubled by nausea?	15	ns	17
Troubled by vomiting?	9	ns	10
Different analgesia next time?	2	ns	3

the 39 reduced doses in the MST group were significantly fewer than the 54 reduced doses in the i.m. morphine group (chi squared 4.57, $P < 0.05$).

Table III shows the results of the "Patient Satisfaction Questionnaire" from the 1st day after operation. The results obtained on the 2nd day after operation are similar and have not been included.

Serum morphine concentrations were measured in 12 patients (table IV). There was a significantly lower serum morphine concentration in the MST group at 08.00 h compared with the data for the i.m. morphine group at the same time, despite the additional administration of a mean dose of 6.4 mg of parenteral morphine in the MST group and the lack of omission of any of the prescribed oral doses (table IV). The concentration of morphine in the MST group at 08.00 h was also significantly smaller than the data for both i.m. and oral morphine at 16.00 h. There was no significant difference between the i.m. and MST group at 16.00 h.

There were six withdrawals from the trial. All these were in the group receiving i.m. morphine. The reasons given were vomiting (three cholecystectomy, one hysterectomy), insufficient analgesia (one hysterectomy) and both insufficient analgesia and vomiting (one hysterectomy). The difference in withdrawal rate was significant.

TABLE IV. *Data relating to 12 patients in whom measurements of serum morphine concentration were obtained. Values expressed as mean (range)*

	MST ($n = 6$)	Morphine i.m. ($n = 6$)
Time from surgery to 0800 h (h)	18.9 (16.5–21.5)	17.8 (16.8–20.8)
Mean dose of prescribed morphine administered (mg)		
to 08.00 h	90 (60–100)	37.5 (25–50)
09.00–16.00 h	33.2 (20–40)	13 (10–20)
Mean dose of supplementary morphine administered (mg)		
to 08.00 h	6.4 (0–20)	5 (0–10)
09.00–16.00 h	1.6 (0–10)	00 (0)
Total morphine administered (mg)		
to 08.00 h	96.4	42.5
to 16.00 h	131.5	56.5
Serum morphine concn (ng ml^{-1})		
08.00 h	1.9 (0–8.2)	19.5 (8.4–33.7)
16.00 h	19.5 (10.7–31.4)	17.5 (10.0–29.9)

DISCUSSION

These results have demonstrated that it was possible to produce acceptable analgesia with MST after abdominal surgery, provided that provision was made for the administration of supplementary parenteral doses of morphine. There was a remarkable similarity in the pain scores seen in the MST group in comparison with the i.m. morphine group. However, if the unwanted effects of morphine (sedation, nausea and vomiting) are summated, differences between the two groups are readily apparent in the earlier part of the 1st day after operation — notably that for similar degrees of analgesia there were fewer side-effects in the MST group.

Our choice of a 4-hourly dose regimen for MST requires some explanation since the long duration of action of MST could permit cumulation. However, the use of a 4-hourly dose facilitated the use of a double-blind double-dummy comparison and, in addition, it was felt that the instruction to nursing staff to halve or omit *small* doses given frequently permitted finer adjustment of the total dose to meet individual variations in pharmacodynamics.

Although pharmacokinetic studies from our Department have suggested that the bioavailability of MST is 20% following a single dose (Vater et al., 1984), the decision to compare MST 20 mg with i.m. morphine 10 mg was based upon our earlier clinical studies. These suggested a clinically effective ratio of 2:1 MST:morphine for continuing doses over 24–48 h (Fell, Chmielewski and Smith, 1982). The results of the present study also suggest an *analgesic* ratio closer to 2:1 than to 5:1 for administration over a sustained period of time.

With patient controlled administration, a correlation has been demonstrated between plasma opioid concentration and effective analgesia (mean effective analgesic concentration or MEAC) (Tamsen et al., 1982). Individual patients request additional doses of analgesia when the plasma concentration of opioid decreases below MEAC. Although this is a relatively constant value for the individual, there is a five-fold variation between individuals (Tamsen et al., 1982). In the present study, there was a considerable difference between the mean serum concentrations of morphine in the two groups at 08.00 h and yet the levels of analgesia were similar — that in the MST group (at 08.00 h) being comparable to analgesia provided by i.m. patient-controlled analgesia (Harmer et al., 1983). In addition, the MEAC for morphine is approximately 16 ng ml^{-1} (HPLC technique) and it is therefore difficult to account for the satisfactory analgesia achieved in the MST group at 08.00 h.

There are two possible explanations for this anomaly. First, that satisfactory analgesia at 08.00 h was achieved by a placebo effect. It is known that, after major surgery, some 30% of patients may achieve adequate analgesia without opioids (Beecher, 1959) and that placebos are capable of exerting a very potent analgesic action (Beecher, 1955). It is possible that, in the circumstances of this trial, a potent placebo effect may have been induced.

A second highly speculative reason for the differences between analgesia and serum concentration may be a result of biotransformation. One significant breakdown pathway of morphine is by hepatic conjugation. A major metabolite is morphine-3-glucuronide (M3G) (Boerner, Abbott and Roe, 1975), which is not known to possess any analgesic properties. In addition, a smaller proportion of the administered dose is conjugated to morphine-6-glucuronide (M6G). M6G is thought to be three to four times more potent as an analgesic than is free morphine, and to possess a longer half-life, although it may cross the blood–brain barrier slowly. All the administered dose of MST will have passed through the liver before becoming available systemically. It is possible that, in the MST group, some analgesia was provided by M6G. It is difficult to test this hypothesis because of the difficulties inherent in the analysis of M6G, but Svensson and his colleagues (1982) suggested that M6G is the major metabolite of the long term oral administration of morphine.

The very low concentration of free morphine in the MST group at 08.00 h in comparison with the value at 16.00 h and in comparison with the 08.00-h value in the i.m. morphine group is a matter of some concern, since it suggests that there is reduced absorption of MST in the early postoperative period. It has been shown recently that, although morphine administered orally (as MST 20 mg) has no effect on gastric emptying, systemic morphine in a dose of 10 mg causes marked delay in emptying (Park and Weir, 1984). It has been known for some time that anaesthesia (Nimmo, 1984) and systemic opioids delay gastric emptying and it is likely that the low concentration of MST seen in our patients at 08.00 h was produced by the effect of anaesthesia and intraoperative i.v. opioids on systemic absorption. The high concentration of morphine seen in the MST group at 16.00 h is also worrying. If we are comparing 4 mg of available free morphine (MST) with 10 mg (i.m. morphine), the only explanation for the similar concentrations at 16.00 h is that some "dumping" occurred after the delay in gastric emptying had decreased.

The design of our study did not allow us to examine the first 18 h of the postoperative period and we are unable to comment directly on the *quality* of analgesia before 08.00 h on the 1st day after operation. Nonetheless, the significantly greater number of escape doses of morphine required in the MST group and the significantly higher pain scores at 08.00 h suggest that the analgesia provided by *MST alone* in the early postoperative period was suboptimal. Only by provision of supplementary doses of morphine did patients in both groups achieve the same level of overall postoperative comfort (table II).

Peak expiratory flow rates were similar in both groups. Our data support earlier work (Spence and Smith, 1971) showing only a slow improvement in lung function during the early postoperative period in spite of analgesia which is rated as acceptable by the patient. A correlation between LAPS and PEFR was demonstrated, confirming earlier studies (Ellis et al., 1982).

Previous studies have suggested that MST may be used to provide satisfactory postoperative analgesia. However, the results of the present study suggest that enthusiasm for this method should be tempered with considerable caution. From our preliminary measurements of plasma morphine concentration, it would appear that there may be little absorption of MST in the period immediately after anaesthesia with systemic opioids. This may produce suboptimal analgesia, but also cause the unacceptable risk of belatedly dumping a large dose of drug from the stomach when gastrointestinal motility increases. However, it should be noted that there was no evidence in the present study for excessive sedation in the MST group in the second 24 h.

These observations regarding dumping of MST are clearly speculative, since we measured plasma morphine in relatively few patients. We would suggest that further studies of the bioavailability of MST in the postoperative period are required before recommendations may be made regarding the routine use to provide analgesia at that time.

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AGE AND NATURE OF OPERATION INFLUENCE THE PHARMACOKINETICS OF MIDAZOLAM

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SUMMARY

The pharmacokinetics of midazolam were studied in surgical patients given 0.3 mg kg^{-1} i.v. for either the induction of anaesthesia, or post-operative sedation following cardiopulmonary bypass. The short elimination half-life of midazolam (2.4 h in patients < 50 yr undergoing minor surgery) was significantly, although not markedly, prolonged with age (4.1 h in patients > 50 yr undergoing minor procedures) and by the nature of the operation (3.8 h after major operative procedures). These changes were the result of alterations in clearance and volume of distribution with age, and in volume of distribution with nature of operation.

Midazolam, in doses of 0.1–0.2 mg kg^{-1}, is used primarily to provide sedation during endoscopy, dentistry or other procedures carried out under regional analgesia. A higher dose (0.3 mg kg^{-1} i.v.) has met with some success as an anaesthetic induction agent, particularly in poor-risk patients. However, since no data are available on the influence of the surgical procedure on the pharmacokinetics of this agent, this aspect is addressed in the present report. In common with other benzodiazepines (Klotz et al., 1975; Klotz and Muller-Seydlitz, 1979; Mattila and Larni, 1980; Shader, Greenblatt and Harmatz, 1977), the elimination of midazolam has been reported to be longer in elderly patients (Collier et al., 1982); this point is examined in greater detail.

PATIENTS AND METHODS

Studies were conducted in 67 fit adults scheduled for routine surgery, and in seven who had undergone coronary artery surgery under cardiopulmonary bypass. None of the patients had received a benzodiazepine in the period immediately preceding the study. They were divided into young (<50 yr) and older (50+ yr) age groups, and according to the nature of the operation, those undergoing minor or major procedures. (Patients having cardiac surgery were in the older age group.) Major procedures were intra-abdominal or intrathoracic and minor, gynaecological or endoscopic. Premedication, if used, was with an opiate, benzodiazepines being avoided. Anaesthesia was induced with midazolam 0.3 mg kg^{-1} in all patients except those undergoing cardiac surgery, when it was given for sedation following operation. Anaesthesia was maintained with 67% nitrous oxide in oxygen, supplemented in the major procedures with intermittent doses of thiopentone, Althesin or an opiate. A non-depolarizing neuromuscular blocking drug was administered and controlled ventilation established. Physiological saline or a solution of sodium lactate compound (BNF) was infused in patients requiring major operations, but was given very slowly during the first 1 h following induction. A few patients required blood transfusion, but those receiving more than 800 ml during the first 12 h were excluded from the study. Patients undergoing cardiac surgery were transfused with physiological

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TABLE I. *Patient characteristics in young (< 50 yr) patients undergoing minor and major operative procedures, and in older (50+yr) patients following cardiac surgery. †Figures in parentheses refer to additional patients excluded because of atypical $T_{\frac{1}{2}}^{\beta}$ as discussed in the text*

Operation	Patients	*n*†	Women	Age (yr)	Weight (kg)
Minor	Young	18 (1)	17	33±2.2	63±1.9
	Older	7 (0)	7	69±4.2	66±1.8
Major	Young	24 (1)	23	35±1.2	62±2.0
	Older	14 (2)	9	64±3.1	62±2.9
Post-cardiac	Older	7 (2)	3	60±2.7	72±4.0

saline, sodium lactate compound (BNF), plasma and whole blood to maintain their haemodynamic indices within their normal range. As far as possible arterial pH and $P\text{CO}_2$, which were monitored frequently, were kept within their normal ranges during the operation.

Blood was drawn for the estimation of plasma midazolam either from a cannula inserted to the arm contralateral to that used for the injection of midazolam, or from an arterial cannula which had been inserted to a radial artery as part of the anaesthetic procedure. Samples were taken at 0, 7.5, 15, 30, 45, 60 and 90 min and at 2, 4, 6, 9 and 12 h after midazolam in patients undergoing minor and major operations and at 0, 7.5, 15, 30, 60 and 90 min and 2, 4, 6, 8, 10 and 12 h in patients undergoing cardiac surgery. After separation, the samples of plasma were stored at −20 °C before plasma midazolam was estimated using gas–liquid chromatography as described by Gamble and colleagues (1975) and Howard and co-workers (1978). In our laboratory the coefficient of variation of the method of estimation was between 3.5 and 8.5%.

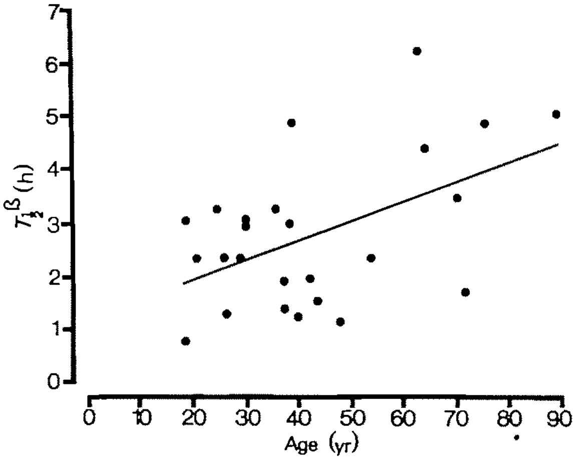

FIG. 1. Correlation of elimination half-life ($T_{\frac{1}{2}}^{\beta}$) of midazolam with age in all patients undergoing minor operative procedures. ($T_{\frac{1}{2}}^{\beta} = 0.038 \times \text{age} + 1.95$; $r = 0.535$; $P < 0.01$.)

Elimination half-life ($T_{\frac{1}{2}}^{\beta}$), clearance (*Cl*) and volumes of distribution ($V\text{d}^{\text{area}}$ and $V\text{d}^{\text{ss}}$) were calculated using standard non-compartmental methods (Benet and Galeazzi, 1979; Rowland and Tozer, 1980). Distribution half life ($T_{\frac{1}{2}}^{\alpha}$) was obtained from a biexponential fit to the plasma concentration data using a non-linear least squares regression program on an Apple II computer.

RESULTS

Table I shows the patient characteristics in the five series, all of which were broadly comparable, although the mean weight in the patients undergoing cardiac surgery was greater than in the other groups, a possible reflection of the greater proportion of men in that group.

The values of $T_{\frac{1}{2}}^{\beta}$ obtained from the biexponential fit did not differ significantly from those obtained using the non-compartmental approach.

TABLE II. *Mean (± SEM) distribution ($T_{\frac{1}{2}}^{\alpha}$) and elimination ($T_{\frac{1}{2}}^{\beta}$) half-lives, clearance and volumes of distribution ($V\text{d}^{\text{area}}$ and $V\text{d}^{\text{ss}}$) in young (< 50 yr) and older (50+ yr) patients receiving midazolam 0.3 mg kg^{-1} for minor and major operations, and for sedation following cardiac procedures*

			Half-life			Volume of distribution	
Operation	Patients	*n*	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (h)	Clearance (ml kg^{-1} h^{-1})	$V\text{d}^{\text{area}}$ (litre kg^{-1})	$V\text{d}^{\text{ss}}$ (litre kg^{-1})
Minor	Young	18	18.5±2.27	2.37±0.242	386±43.9	1.17±0.121	1.10±0.151
	Older	7	17.9±4.02	4.10±0.592	284±27.5	1.60±0.223	1.34±0.159
Major	Young	24	30.5±2.67	3.76±0.330	412±40.0	2.06±0.223	1.67±0.160
	Older	14	28.6±3.71	3.89±0.431	347±37.1	1.86±0.243	1.54±0.193
Post-cardiac	Older	7	30.0±3.59	4.62±0.394	374±31.5	2.39±0.097	1.39±0.147

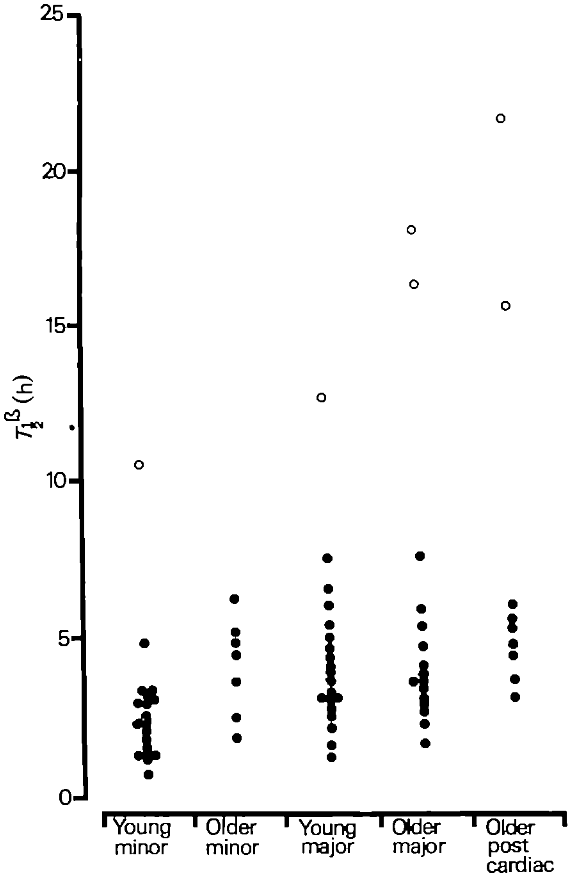

FIG. 2. Individual elimination half-lives ($T_{\frac{1}{2}}^{\beta}$) in young (< 50 yr) and older (50+ yr) patients receiving midazolam 0.3 mg kg^{-1} for minor and major surgical procedures, and in older (50+ yr) patients receiving the drug for sedation following cardiac surgery. The open circles represent those patients with an atypically long half-life $T_{\frac{1}{2}}^{\beta}$).

In no patient was there any evidence of a third exponential phase describing the disposition of the drug.

Distribution half-life ($T_{\frac{1}{2}}^{\beta}$) was significantly longer in those patients undergoing a major procedure ($P < 0.005$) or cardiac surgery ($P < 0.002$) when compared with patients undergoing minor operations. Age had no effect within any operation group (table II).

Elimination half-life ($T_{\frac{1}{2}}^{\beta}$) was longer in the older as compared with the younger patients having minor operations (table II) and in this operation group $T_{\frac{1}{2}}^{\beta}$ correlated well with age (fig. 1) ($r = 0.5$; $P < 0.01$). This effect of age was not seen in patients having major or cardiac operations. In six patients not included in these data, $T_{\frac{1}{2}}^{\beta}$ was much longer than that obtained in the rest of the series, the results being well outside the range which could be explained by laboratory errors, over or under infusion, hyperventilation or blood loss, and will be discussed later.

Although the average clearances were smaller in the older patients within each group, the differences were not significant. Pooling younger and older patients in the two operation groups revealed a significantly greater clearance in the younger (402 ± 29 ml kg^{-1} h^{-1}) than in the older (325 ± 25 ml kg^{-1} h^{-1}) patients ($P < 0.05$).

The average volume of distribution, calculated by two methods (Vd^{area} and Vd^{ss}), was greater in older patients undergoing minor operations than in the equivalent younger age group, but the difference did not reach significance ($P < 0.1$ for Vd^{area}). This difference was not seen in patients undergoing major operations.

Elimination half-life ($T_{\frac{1}{2}}^{\beta}$) was longer in young patients undergoing minor as compared with major procedures ($P < 0.05$) in spite of a slightly higher clearance. The volume of distribution calculated by both methods (Vd^{area} and Vd^{ss}) was greater ($P < 0.02$) when associated with major as compared with minor operations in the young age group. There were no significant differences in $T_{\frac{1}{2}}^{\beta}$, clearance, Vd^{area} or Vd^{ss} with major as compared with minor operations in the older patients.

Compared with the older patients undergoing minor operations, those from the same age group who had been subjected to cardiopulmonary bypass showed a significantly larger Vd^{area} ($P < 0.01$) and a greater clearance ($P < 0.05$). This resulted in a non-significant increase in $T_{\frac{1}{2}}^{\beta}$.

The pharmacokinetic parameters of six patients with the atypically long elimination half-lives, illustrated in figure 2, are shown in table III. They occur in all operation groups and in both age groups. In some instances the long $T_{\frac{1}{2}}^{\beta}$ could be attributed to a low clearance, or a large volume of distribution, but in others it appeared to be the result of a combination of the two.

DISCUSSION

Elimination half-life is only inversely proportional to clearance if the volume of distribution is unchanged; similarly, it is only directly proportional to the volume of distribution if the clearance is unchanged. A change in either, or a combined change in clearance and volume of distribution in opposite directions would account for changes in

TABLE III. *Atypical elimination half-lives* ($T_{\frac{1}{2}}^{\beta}$) *in six patients receiving midazolam* 0.3 *mg kg*$^{-1}$ *i.v., with corresponding distribution half-life* ($T_{\frac{1}{2}}^{\alpha}$)*, clearance and volumes of distribution* (Vd^{area} *and* Vd^{ss})

	Patients		Half-life			Volume of distribution	
Operation	Sex	Age (yr)	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (h)	Clearance (ml kg^{-1} h^{-1})	Vd^{area} (litre kg^{-1})	Vd^{ss} (litre kg^{-1})
Minor	F	45	33.6	10.5	324	4.91	3.28
Major	F	31	30.3	13.7	99	1.96	1.73
	F	56	21.5	18.6	270	7.24	5.04
	F	52	45.6	16.4	156	3.70	2.81
Post-cardiac	F	48	42.6	22.2	91	5.06	5.81
	M	64	31.6	15.7	260	5.89	4.02

elimination half-life. A change in elimination half-life does not discount changes in clearance and volume of distribution in the same directions. From our results, it would appear likely that the prolongation of the elimination half-life seen with age was the result of a combination of a decrease in clearance and an increase in volume of distribution, while that attributable to the nature of this surgery was the result of an increase in volume of distribution only.

Midazolam is cleared from plasma almost exclusively by liver oxidative processes involving cytochrome P450, less than 1% appearing unchanged in the urine (Allonen, Ziegler and Klotz, 1981; Smith, Eadie and Brophy, 1981). The metabolites are conjugated quickly, contributing little to the pharmacological effect. The hepatic extraction ratio of midazolam varies from 0.3 to 0.7, the liver clearing one-third to two-thirds of the blood passing through it. With such extraction ratios, the clearance of drugs given i.v. depends on both the intrinsic hepatic clearance and the hepatic blood flow (Rowland, Benet and Graham, 1973). The extensive binding of midazolam to serum albumin (Allonen, Ziegler and Klotz, 1981), leaving only 2–5% as free drug, implies that it must leave the binding sites as it is being cleared from plasma by the liver, but this does not restrict overall clearance (Wilkinson and Shand, 1975). Since only free drug will leave the blood stream, distribution acts only on the free fraction. A decrease in serum albumin concentration or a decrease in binding may increase the already high volume of distribution for midazolam by allowing faster and more extensive redistribution. Changes in the size of biological fluid compartments, and alterations in regional blood flow and in membrane permeability can also alter the rate and extent of redistribution. Thus the disposition of midazolam may be altered by factors influencing liver enzyme activity, plasma protein binding, liver blood flow and tissue perfusion.

As cardiac output decreases with increasing age, more blood flows to the brain, heart and muscle, reducing the proportion to liver (Bender, 1965). A decrease in the size of the liver with respect to body weight, lower cytochrome P450 content and lower liver microsomal enzyme activity would all contribute to a decrease in clearance (Novak, 1972). Body fat, which will bind a lipid soluble drug, increases with age and will increase the volume of distribution. Decreases in the plasma protein concentration and reductions in the strength and extent of binding increase the fraction of free drug.

During surgery, anaesthesia and controlled ventilation may decrease hepatic, and alter regional, blood flow (Smith, Zwart and Benchen, 1972). The fact that an age-related increase in $T_{\frac{1}{2}}^{\beta}$ is not seen in major surgery, may be the result of a relatively smaller change in blood flow distribution resulting in minimal changes in the volume of distribution. The use of electrolyte solutions, although minimized in this study, may temporarily decrease the concentration of plasma proteins, and the redistribution of this fluid may then alter the redistribution of drug. There would be a natural tendency for anaesthetists to restrict fluid and electrolyte therapy in the elderly, possibly contributing to the smaller increase in *Vd* in these patients. Midazolam lost with blood may increase the apparent volume of distribution in major operations. Postoperative pain, with an increase in catecholamine concentrations and cold, may alter tissue perfusion. The absence of any overall change in clearance in patients undergoing a major procedure during the 12 h of the study does not preclude minute-to-minute changes resulting

TABLE IV. *Comparison of mean (± SEM) elimination half-lives ($T_{\frac{1}{2}}^{\beta}$), clearance and volumes of distribution (Vd^{area} and Vd^{ss}) in young (< 50 yr) and older (50+ yr) patients undergoing minor procedures, with two other studies in similar patients*

	Patients' age (yr)	n	Half-life $T_{\frac{1}{2}}^{\beta}$ (h)	Clearance (ml kg^{-} h^{-1})	Volume of distribution	
					Vd^{area} (litre kg^{-1})	Vd^{ss} (litre kg^{-1})
This study	< 50	18	2.4 ± 0.24	386 ± 44	1.2 ± 0.12	1.1 ± 0.15
	50+	7	4.1 ± 0.59	284 ± 28	1.6 ± 0.22	1.3 ± 0.16
Collier and others (1982)	< 50	10	2.8 ± 0.28	450 ± 35	1.8 ± 0.16	1.7 ± 0.10
	60+	10	4.3 ± 0.62	430 ± 51	2.8 ± 0.27	2.5 ± 0.20
Avram, Fragen and Caldwell (1983)	22–30	11	2.7 ± 0.24	436 ± 38		1.1 ± 0.05
	50–60	11	3.2 ± 0.21	419 ± 25		1.4 ± 0.09

from any decrease in hepatic blood flow during the period of anaesthesia and surgery.

In spite of the very low temperatures (20 °C) used during cardiac operations, the liver is subsequently well able to handle the midazolam presented to it as seen by the adequate clearance in patients following cardiopulmonary bypass.

The pharmacokinetics of a drug, although necessary for an understanding of drug action, may not relate closely to the pharmacodynamic response. Although plasma drug concentrations decrease rapidly, the binding of midazolam to brain and other receptors may result in an action out of proportion to the half-life of the drug. This is seen especially in the elderly, where small doses can produce a profound and prolonged effect. Care is, therefore, necessary in the elderly and, as shown in this study, in patients subjected to anaesthesia and major surgical procedures.

Table IV compares our results with those of two other groups who studied the effects of age in patients undergoing minor operations. From our own Department, in a separate study, Collier and colleagues (1982) have also shown a longer elimination half-life (2.8–4.3 h) in older patients undergoing minor operations, and attributed this to an increase in the volume of distribution. Avram, Fragen and Caldwell (1983) found an increase in the volume of distribution between similar groups of patients, but the small increase in elimination half-life (2.7–3.2 h) was not significant. The overall clearance (357 ml kg^{-1} h^{-1}) obtained in the present study is lower than the 440 ml kg^{-1} h^{-1} noted by Collier and colleagues (1982) and this may be the result of their use of halothane, which can displace drugs from serum albumin (Dale and Nilsen, 1984).

The six patients who showed atypically long elimination half-lives are worthy of comment. Their values are well outside our range of experimental error and their significance has yet to be determined. Evans and co-workers (1980) have described a sub-population of poor metabolizers of debrisoquine by hepatic oxidation possibly involving cytochrome P450, occurring in 8.9% of a survey of 258 unrelated white British subjects. A similar sub-group may exist for the benzodiazepines, but this has not been described previously.

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PHARMACOKINETICS OF PHENOPERIDINE IN ANAESTHETIZED PATIENTS UNDERGOING GENERAL SURGERY

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SUMMARY

The pharmacokinetics of phenoperidine have been studied in five anaesthetized patients receiving a 2-mg bolus dose i.v. Plasma concentrations were measured using a sensitive radioimmunoassay method. The distribution of phenoperidine was described according to a two-compartment open model. The mean distribution half-life ($T_{\frac{1}{2}}^{\alpha}$) *for the five patients was short (2.2 min); the mean elimination half-life* ($T_{\frac{1}{2}}^{\beta}$) *was 193 min. The mean whole body clearance was 22 ml* min^{-1} kg^{-1} *and the apparent steady state distribution volume* (V^{ss}) *was 5.7 litre* kg^{-1}*. Secondary concentration peaks occurred in all patients; in two patients these were substantial and occurred 80 min after injection.*

Although the pharmacokinetics of phenoperidine have been studied in volunteers and anaesthetized patients (Milne et al., 1980; Isherwood et al., 1981; Calvey et al., 1983) the results have been conflicting—especially in regard to the occurrence of secondary concentration peaks. A radioimmunoassay was used to assess the pharmacokinetics of phenoperidine in anaesthetized patients undergoing general surgery, and the results are reported here.

PATIENTS AND METHODS

Five patients (ASA class I or II) were studied following informed consent and institutional approval; they underwent non-haemorrhagic orthopaedic or gynaecological procedures: details of the individual patients are presented in table I. No patient had any cardiac, hepatic or renal abnormality; none was receiving regular medication, in particular with cimetidine or an antacid preparation.

Patients were premedicated with diazepam 10 mg and atropine 0.5 mg i.m. 1 h before surgery. Induction of anaesthesia was with thiopentone 5–7 mg kg^{-1} and intubation was achieved with the aid of suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with 60% nitrous oxide in oxygen. Ventilation was controlled in all patients and pancuronium 0.1 mg kg^{-1} administered to provide neuromuscular blockade. No patient received naloxone at the end of surgery.

Phenoperidine 2 mg was administered 10 min following induction and before the surgical incision. During surgery, if analgesia appeared to be inadequate, fentanyl was administered.

Blood was withdrawn from a vein in the contralateral arm 2, 4, 6, 10, 20, 40, 60, 80, 120, 180, 240, 300, 360 min following the injection. Plasma was separated by immediate centrifugation and stored at −30 °C pending subsequent determination of the phenoperidine concentration, by radioimmunoassay. This method uses antiserum obtained by the immunization of rabbits with the combination of serum albumin and a cetoxime derivative of phenoperidine. Cross-reaction (ID_{50}) is expressed as the molar reaction of the amount of the compound required to inhibit ^{3}H-phenoperidine binding to antibodies by 50% relative to

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TABLE I. *Patient details*

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	Duration of anaesth. (min)	Surgical procedure
1	F	50	167	62	120	Hip arthroplasty
2	F	53	163	62	120	Hysterectomy
3	M	54	178	63	180	Laminectomy
4	F	45	158	59	120	Hysterectomy
5	M	47	171	80	150	Laminectomy
Mean		49.8	167.4	66.4	138	
SD		±3.8	±7.6	±7.7	±26.8	

the amount of radioligand. The radioimmunoassay is specific for phenoperidine; ID_{50} for the metabolites of phenoperidine (pethidine, norpethidine) is 40. No cross-reaction has been demonstrated with fentanyl. Plasma phenoperidine concentrations as low as 0.1 ng ml^{-1} can be assayed; in the range phenoperidine 0.1–20 ng ml^{-1}, the coefficient of variation is identical for low and high concentrations (9.2%). Radioactive ^3H-labelled phenoperidine and rabbit antibodies were supplied by Janssen Pharmaceutica (Beerse, Belgium).

The important secondary concentration peaks, widely variable in time, made the evaluation of the pharmacokinetics for each patient impossible except for the determination of total plasma clearance. We had to resort to using the mean curve of the phenoperidine concentration with a non-weighted regression analysis; calculations were based on the equation system describing the two-compartment open model.

Results are reported as mean ± SD

RESULTS

Phenoperidine kinetics showed considerable individual variability. Kinetics observed in patients 1 and 2 are presented in figure 1; a rapid decrease in concentration, corresponding to the period of distribution, was followed by a transient but substantial increase in phenoperidine concentration occurring approximately 80 min after injection. At that time, the phenoperidine concentration was equal to that observed 2–6 min following injection (8.8 and 6.4 ng ml^{-1}, respectively, for patients 1 and 2). A second concentration peak occurred in patient 2, 240 min after injection. The kinetics obtained in patients 3, 4 and 5 are presented in figure 2; they show different, less important secondary peaks. The mean curve is presented in figure 3.

The decline in the plasma concentrations of phenoperidine with time can be expressed as a biexponential equation of the form:

$$C_P(t) = Ae^{-\alpha t} + Be^{-\beta t}$$

where $C_P(t)$ is the plasma concentration of phenoperidine at time t; A and B(ng ml^{-1}), α and β (min^{-1}) are hybrid constants. The following equation describes the phenoperidine plasma concentration decay curve:

$$C_P(t) = 28.5e^{-0.309t} + 4.65e^{-0.0036t}$$

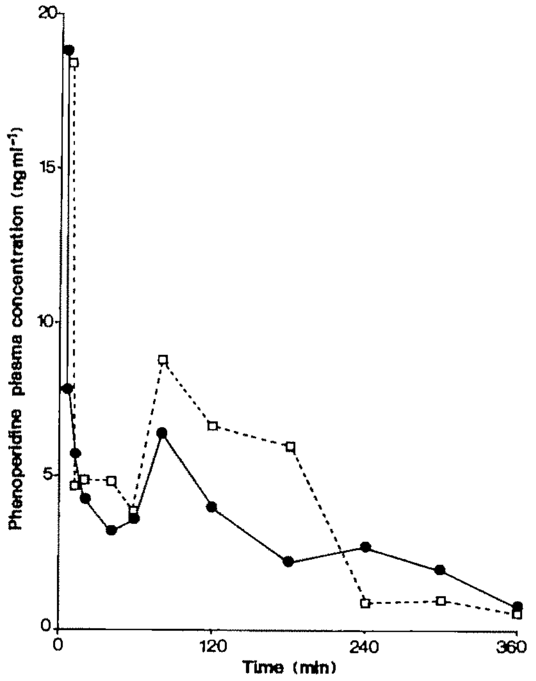

FIG. 1. Individual phenoperidine plasma concentrations following i.v. injection of 2 mg to patient 1 (——) and patient 2 (——).

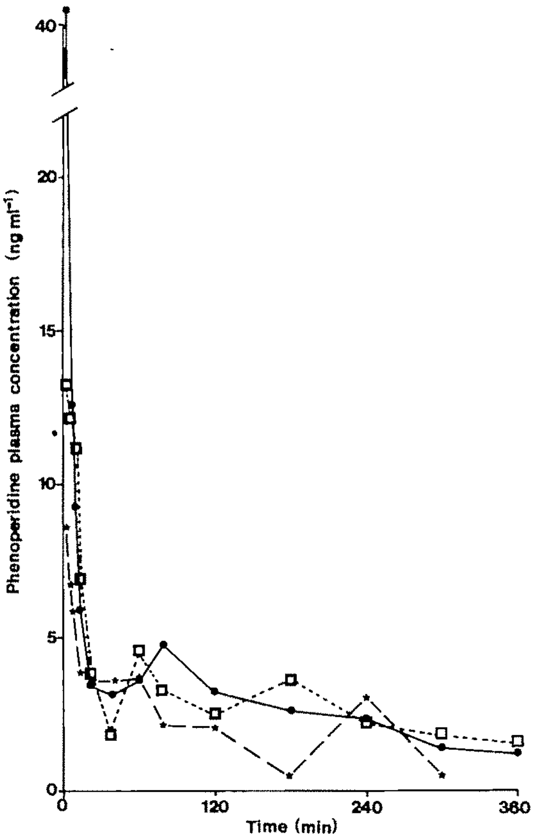

FIG. 2. Individual phenoperidine plasma concentrations in patients 3, 4 and 5.

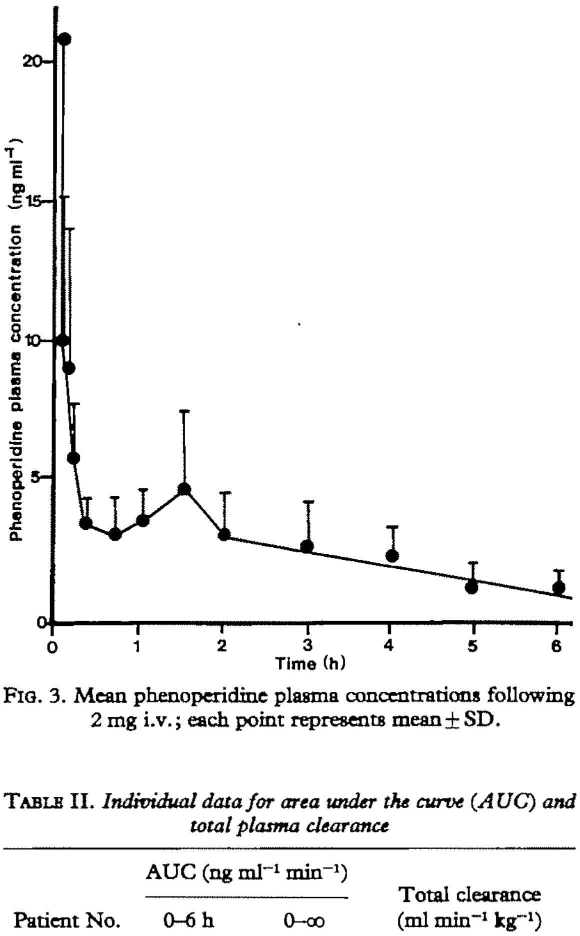

FIG. 3. Mean phenoperidine plasma concentrations following 2 mg i.v.; each point represents mean ± SD.

TABLE II. *Individual data for area under the curve (AUC) and total plasma clearance*

Patient No.	AUC ($ng\ ml^{-1}\ min^{-1}$) 0–6 h	AUC ($ng\ ml^{-1}\ min^{-1}$) 0–∞	Total clearance ($ml\ min^{-1}\ kg^{-1}$)
1	1305	1549	20.8
2	1132	1345	23.9
3	710	843	37.6
4	1102	1560	21.7
5	876	1356	18.4
Mean	1025	1330	24.5
SD	233	291	7.6

The average half-lives for the α and β phases were 2.2 min and 193 min, respectively. The calculated initial volume of distribution (V_1) was 0.9 litre kg^{-1}; the apparent steady state distribution volume (V^{ss}) was 5.7 litre kg^{-1}.

Average whole body clearance (*Cl*), calculated from the mean curve (fig. 3), was 22 ml min^{-1} kg^{-1}. The individual values for the area under the curve (AUC) and for plasma clearance are reported in table II. AUC was extrapolated from t_0 to t_∞ using the mean terminal half-life value (193 min). Whether the individual curves or the mean curve were used, values of plasma clearance were similar (24.5 and 22 ml min^{-1} kg^{-1}, respectively).

DISCUSSION

The elimination half-life of phenoperidine obtained in this study (193 min) is quite different from those reported previously. Milne and colleagues (1980) studied the pharmacokinetics of phenoperidine in anaesthetized patients using a chromatographic method of analysis; they reported an elimination half-life of 90.4 min with values ranging from 47.3 to 162.3 min. Using the same scheme of dosage, Isherwood and co-workers (1981) studied volunteers during a 2-h period of sampling; their estimated mean elimination half-life was 65.9 ± 6.8 min. The plasma clearance reported in the present study can be considered to be greater than that reported by Calvey and associates (1983) on volunteers, since these authors found an equivalent value (24 ml min^{-1} kg^{-1}) for a 3-h period of sampling only.

Differences between previous results and ours could be accounted for by the different periods of sampling, the different methods of analysis or the important individual variability of phenoperidine metabolism (Chan et al., 1983). Considerable variability is obvious in the study by Milne and colleagues (1980). In our study two groups of patients could be distinguished: phenoperidine kinetics were comparable in patients 1 and 2, in whom there were substantial and early secondary peaks, while in patients 3, 4 and 5 the secondary peaks were less marked and occurred later.

The pharmacokinetics of phenoperidine can be compared with those of fentanyl. The elimination half-life of phenoperidine appears to be equal to, or a little shorter than, that of fentanyl, which is generally assumed to be longer than 200 min; for example 219 ± 10 min in volunteers following a 6.4-μg kg^{-1} bolus dose (McClain and Hug, 1980) and 263 ± 49 min in patients with normal hepatic function (Haberer et al., 1982). The apparent steady state distribution volume of phenoperidine (5.7 litre kg^{-1}) was relatively larger than that of fentanyl: 3.44+0.64 litre kg^{-1} in the study by Haberer and colleagues (1982). McClain and Hug (1980) reported fentanyl V^{β} 4 ± 0.2 litre kg^{-1}. Average clearance of phenoperidine (22 ml min^{-1} kg^{-1}) was greater than that of fentanyl (13 ± 0.9 ml min^{-1} kg^{-1} (McClain and Hug, 1980); 10.8 ± 1.2 (Haberer et al., 1982)). The plasma clearance of phenoperidine is also greater than the hepatic plasma flow (900 ml min^{-1} (Ritschel (1980)). Since fentanyl has an important hepatic extraction ratio, phenoperidine can be assumed to have the same profile combined with an extrahepatic elimination. Plasma and tissue esterases are probably responsible for phenoperidine ester hydrolysis, as has been demonstrated for pethidine which is an analogue and metabolite of phenoperidine (Clarke, 1978).

Of the five patients studied, two demonstrated substantial secondary concentration peaks which were greater than 5 ng ml^{-1}, the value considered to be the threshold for the clinical effect of phenoperidine (Milne et al., 1980). Milne and colleagues (1980) were unable to demonstrate any secondary concentration peaks in their initial study in anaesthetized patients. More recently, however, they showed, in volunteers, two secondary concentration peaks occurring 25 and 40 min following injection (Calvey et al., 1983). Although such secondary concentration peaks have been reported in several studies with fentanyl (McQuay et al., 1979; Stoeckel, Hengstmann and Schuttler, 1979) they have, as yet, not been noted with alfentanil (Stanski and Hug, 1982).

Therefore, it can be assumed that only opiates with a large volume of distribution produce secondary concentration peaks. Secondary peaks appear to be greater with phenoperidine than with fentanyl; this could also be a consequence of the larger volume of distribution of phenoperidine. The actual mechanism(s) of these secondary peaks is still uncertain. Gastric secretion of pethidine (Gessner et al., 1976; Dunkerley et al., 1977; Trudnowski and Gessner, 1980), methadone (Lynn et al., 1976) and fentanyl (Stoeckel, Hengstmann and Schuttler, 1979) has been shown. The later enteral reabsorption could explain secondary peaks of concentration observed following the administration of fentanyl (McQuay et al., 1979; Stoeckel et al., 1982) and this has been confirmed by studies using cimetidine or an antacid preparation. Lauven and co-workers (1981), using prophylactic administration of cimetidine, found no secondary peak with fentanyl, and Calvey and colleagues (1983) undertook a similar study using an antacid and phenoperidine. The quantitative effect of gastric secretion–enteral reabsorption is questionable. The gastric volume is decreased in a fasted patient and, consequently, the quantity of opiate available for reabsorption is small (Gessner et al., 1976). The first-pass effect is important for morphine-like compounds: for example systemic bioavailability of oral phenoperidine is about 10–13% (Calvey et al., 1983).

Thus other mechanisms must be suggested, such as a washout from tissues similar to that which follows the release of a tourniquet (Lehman, Freier and Daub, 1982); the high distribution volumes of fentanyl and phenoperidine are consistent with such washout from reservoirs. On the other hand, modifications of plasma pH could also explain the occurrence of secondary concentration peaks (Ainslie, Eisele and Corkill, 1979; Cartwright et al., 1983).

The clinical relevance of secondary peaks of fentanyl has been studied previously (McQuay et al., 1979; Stoeckel, Hengstmann and Schuttler, 1979; Stoeckel et al., 1982). Stoeckel and associates (1982) demonstrated, in volunteers, a weak relationship between the secondary peaks of fentanyl and the magnitude of respiratory depression. In two of our patients, the secondary peaks associated with phenoperidine were significant and occurred relatively early; since these could conceivably induce respiratory depression, the need for close postoperative surveillance is highlighted again.

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PHARMACOKINETICS OF PHENOPERIDINE IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS

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SUMMARY

Phenoperidine concentrations were studied, using radioimmunassay, in five patients submitted to coronary artery bypass graft surgery. Administration of phenoperidine consisted of a 5-mg bolus dose followed by constant infusion of 5 mg h⁻¹. Before cardiopulmonary bypass, phenoperidine concentrations were stable in an individual patient, but there was a large scatter between patients. The concentrations decreased immediately following the start of the bypass, but this decrease was short. During cardiopulmonary bypass, the phenoperidine concentrations increased progressively and were greater at the end of the bypass than before it. The increase in concentration continued following the discontinuation of bypass. The ratios of change of the observed results were in accord with a theoretical evaluation, although the observed concentrations were all greater than those calculated, except at one point. This difference in phenoperidine concentration is probably related to an alteration of liver plasma flow. Haemodilution as a result of the priming of the cardiopulmonary bypass circuit played only a transient role.

Extracorporeal circulation is associated with substantial alterations to the pharmacokinetics of a number of drugs (Holley, Ponganis and Stanski, 1982), the modifications being caused by several factors: systemic arterial hypotension and alterations in regional blood flow, haemodilution, hypothermia and the isolation of the lung. The pharmacokinetics of fentanyl have been studied during cardiac procedures which involved cardiopulmonary bypass (Bovill and Sebel, 1980; Koska, Romagnoli and Kramer, 1981; Howie et al., 1982; Sprigge et al., 1982) in investigations which used either a single bolus dose or a constant infusion of the drug. We have performed a study of the pharmacokinetics of phenoperidine (bolus dose followed by a constant infusion) during cardiac surgery under cardiopulmonary bypass.

PATIENTS AND METHODS

Five patients, suffering from coronary artery disease but with normal ejection fractions, were studied after informed consent and institutional approval had been given. All patients were maintained on their preoperative medications until the night before surgery, except for beta-adrenergic blocking drugs, calcium antagonists and nitrate preparations which were continued up to the time of surgery. No patients received cimetidine or presented with hepatic or renal insufficiency.

The anaesthetic management was that used in our institution for such patients. Patients were premedicated with diazepam 10 mg and atropine 0.5 mg i.m. 1 h before surgery. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 5 µg kg^{-1}; intubation of the trachea was facilitated by suxamethonium 1 mg kg^{-1}, and anaesthesia was maintained with 50% nitrous oxide in oxygen. Pancuronium was administered to produce and maintain neuromuscular blockade. The administration of phenoperidine was initiated 30 min following induction as a bolus dose of 5 mg followed immediately by an infusion of 5 mg h^{-1} until 20–70 min after the end of the cardiopulmonary bypass.

Further injections of other drugs such as fentanyl or droperidol were administered when

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required, depending on the patient's haemodynamic condition.

Arterial pressure (radial artery cannula), central venous pressure and the electrocardiogram were monitored continuously, and acid–base balance, blood-gas tensions, haematocrit and electrolyte concentrations determined at regular intervals.

A Stockert pump and a Bentley Bos 10S oxygenator were used for the cardiopulmonary bypass. Priming consisted of lactated Ringer's solution 1000 ml, 1.4% sodium bicarbonate 250 ml and 2 units of whole blood. Pump flow was kept between 2 and 2.5 litre $\text{min}^{-1}/\text{m}^2$ of body surface. Myocardial protection was by a combination of crushed ice on the heart and infusion of a Breitschneider's solution to the root of the aorta. Central temperature (oesophageal temperature) was decreased to 25.5 °C ± 5.8.

Haemodilution during cardiopulmonary bypass was similar in all patients: mean haematocrit was 37 ± 3% and 26.5 ± 2% before and at the initiation of the cardiopulmonary bypass, respectively. Protein concentrations were, at the same times, 62.7 ± 3 and 41.8 ± 3 g litre^{-1}.

Increase in preload (fresh frozen plasma) was necessary before the termination of bypass.

Blood was withdrawn from the central venous catheter for immediate centrifugation and freezing. The initial sample was drawn 5 min after the start of the phenoperidine infusion and then samples were withdrawn every 5–10 min until the start of cardiopulmonary bypass (30–80 min). Cardiopulmonary bypass lasted between 25 and 80 min; blood samples were withdrawn 2 min after the beginning of bypass and every 5–10 min thereafter. Furthermore, for each patient, two simultaneous samples were withdrawn at the middle of the period of bypass, one from the venous line and the other from the arterial line of the bypass apparatus.

The infusion of phenoperidine was discontinued 20–70 min following bypass. Sampling was continued every 10 min after the end of the cardiopulmonary bypass, and was continued for a particularly long period in patient 2.

The concentrations of phenoperidine were determined by radioimmunoassay using antiserum obtained by the immunization of rabbits with the combination of serum albumin and a cetozime derivative of phenoperidine. This radioimmunoassay is specific for phenoperidine; cross-reaction with phenoperidine metabolites (pethidine, norpethidine) is reduced ($ED_{50} = 40$) and no cross-reaction has been demonstrated with fentanyl (Fischler et al., 1985). Phenoperidine plasma concentrations as low as 0.1 mg ml^{-1} can be assayed; in the range phenoperidine 0.1–20 ng ml^{-1}, the coefficient of variation is identical for low and high concentrations (9.2%). Radioactive ^{3}H-labelled phenoperidine and rabbit antibodies were supplied by Janssen Pharmaceutica (Beerse, Belgium).

Results are reported as mean ± SD.

RESULTS

Details of the patients and types of procedure are presented in table I. Individual results are presented in table II and figure 1.

Five min after the beginning of the administration of phenoperidine, the plasma concentration varied widely from patient to patient, ranging from 14.3 to 53.2 ng ml^{-1} (mean value of 34.5 ± 15.5 ng ml^{-1}). After this initial period, phenoperidine concentrations appeared to be more stable: mean concentration was 27.5 ± 7.4 ng ml^{-1} 10 min after the beginning of the infusion and 27.1 ± 6.7 ng ml^{-1} by 30 min. In three patients the pre-cardiopulmonary bypass period lasted for at least 55 min; at that time the

TABLE I. *Details of patients and operations. (CPB = cardiopulmonary bypass)*

Patient No.	Age (yr)	Sex	Wt (kg)	Operation	Duration of CPB (min)
1	38	M	77	Coronary artery bypass graft (1)	25
2	52	F	78	Coronary artery bypass graft (2)	60
3	65	F	44	Coronary artery bypass graft (2)	80
4	69	M	69	Coronary artery bypass graft (2)	60
5	62	M	62	Coronary artery bypass graft (2)	70
Mean	57.2		66		61
SD	12.4		13.9		23.6

TABLE II. *Individual data obtained before, during and after cardiopulmonary bypass (CPB).* ▬ = *discontinuation of phenoperidine administration*

		Patient No.				
		1	2	3	4	5
0 (= beginning of phenoperidine administration)						
+ 5 min		14.3	24.7	53.2	35.4	44.8
10		19.2	20.4	30.4	31.2	36.4
15	Before CPB	17.5	21.3	35.3		
20		14.6		41.1	29.5	29.2
30		17.6	24.7	34.8	26.0	32.2
40		14.2				27.6
45			21.7	44.2		
50	During CPB	16.5			31.3	30.2
55				28.2		
60		21.1	3.0		38.8	27.9
70		12.5	17.6	19.5		
80		12.9	13.4	32.1	25.5	31.7
90		24.6	23.4			18.7
100		16.8	20.8	27.7	19	31.1
110			25.7	34.2	28.8	24.0
120		17	28.9		26.3	40.6
125				34.1		
130			28.1		23.2	51.5
140			30.2	36.2	27.9	42.2
150			33.7	54.9	28.1	42
160			35.3	50.9		40.1
170	After CPB			42.8	37.3	46.3
180					33.4	
190			32.2	30.1	37.2	44.6
200					32.3	52.7
210					31.9	50.6
220						39.6
230						
240						32.7
250						
260						
280						
300						
320			17.5			
420			15.5			
620			9.8			
1620			1.7			

mean concentration of phenoperidine was 31.6 ± 6.2 ng ml^{-1}.

Two minutes after the beginning of the bypass, the mean concentration was 14.9 ± 7 ng ml^{-1}. For each patient this value was lower than the pre-bypass concentration; but only in patient 2 was the decrease significant (from 21.7 to 3 ng ml^{-1}). The concentrations of phenoperidine increased gradually in all patients following this initial value such that at the end of bypass, in all patients except patient 2, the concentration was higher than it had been just before bypass, the mean value at the end of bypass being 33.5 ± 9.4 ng ml^{-1}.

In all patients the infusion of phenoperidine was continued following bypass for 20–70 min, and phenoperidine concentrations increased during this period. The concentration of phenoperidine was followed up over a prolonged period in patient 2 only: it was 9.8 ng ml^{-1} 420 min and 1.7 ng ml^{-1} 1420 min following the end of the infusion.

Figure 2 shows the remarkable similarity of phenoperidine concentrations between the two sides of the oxygenator.

DISCUSSION

The continuous administration of phenoperidine following a loading dose resulted in a relatively

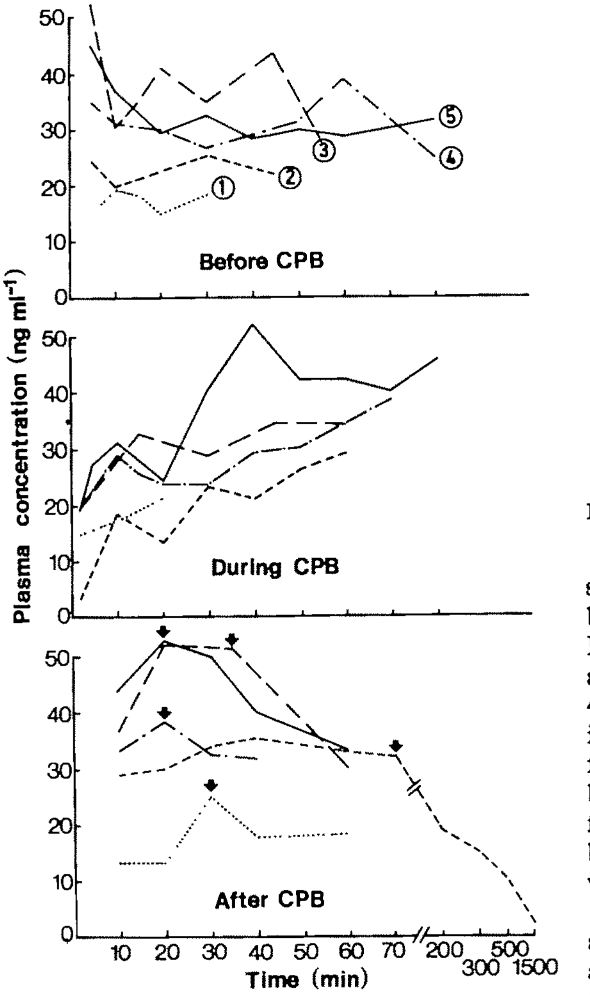

FIG. 1. Phenoperidine concentrations before, during and after the period of cardiopulmonary bypass (the arrow indicates the end of the infusion).

stable mean concentration before cardiopulmonary bypass. The period of bypass induced an initial but brief decrease in concentration which was followed by a progressive increase such that, by the end of bypass, phenoperidine concentrations were higher than before the onset of bypass. A further increase in concentration was noted following the end of bypass. The phenoperidine concentration decreased very slowly after the discontinuation of the infusion.

These results can be compared with those published previously for fentanyl. Using a bolus dose of fentanyl, alterations in the plasma concentration decay curve were demonstrated by several investigators during cardiopulmonary bypass (Lunn et al., 1979; Bovill and Sebel, 1980; Koska, Romagnoli and Kramer, 1981; Howie et al., 1982). Lunn and colleagues (1979) reported a 40% decrease in fentanyl concentration with the initiation of cardiopulmonary bypass and few further changes throughout the remainder of bypass. A 64% decrease in the concentration of fentanyl was obtained when samples obtained before cardiopulmonary bypass were compared with those obtained in the middle (Howie et al., 1982). Sprigge and co-workers (1982) used an approach similar to ours (bolus dose followed by a constant infusion of fentanyl); for each of the three regimens used for constant infusion, a 30% decrease in concentration followed the beginning of cardiopulmonary bypass, but the concentration returned to its pre-bypass values within 30 min.

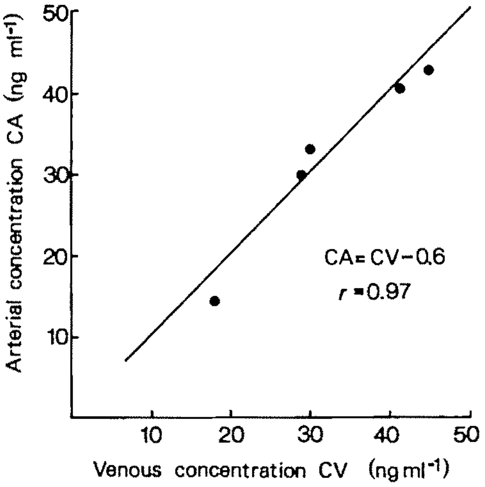

FIG. 2. Correlation between phenoperidine concentrations measured from the arterial and venous sides of the pump.

The effects of cardiopulmonary bypass on the pharmacokinetics of several drugs have been described by Holley, Ponganis and Stanski (1982). Initiation of bypass induces major physiological changes: arterial hypotension and alterations in regional blood flow, haemodilution, hypothermia and isolation of the lung, all of which must be considered when discussing the changes noted in phenoperidine concentration during cardiopulmonary bypass. Furthermore, a theoretical calculation of phenoperidine concentration can be obtained using pharmacokinetic parameters for phenoperidine reported in an accompanying paper (Fischler et al., 1985).

Haemodilution is an important factor (Holley, Ponganis and Stanski, 1982). Priming of the oxygenator induces an acute dilution with an increase in apparent volume of distribution of the drug, a redistribution of drug from tissues back to plasma and a modification of the percentage of free and protein-bound drug. Although this drug-free solution does induce a decrease in drug concentration, the decrease in haematocrit cannot wholly account for the decrease in drug concentration. Proportionally, the decrease in the concentration of fentanyl is always greater than the decrease in haematocrit: a 64% decrease in fentanyl concentration during bypass with a 36% decrease in haematocrit (Howie et al., 1982), and decreases of 53% (drug concentration) and 41% (haematocrit) (Bovill and Sebel, 1980). Our data show that haemodilution plays an important but transitory role: after a brief and substantial decrease in phenoperidine concentration with the initiation of bypass, it increased gradually and after 10 min of bypass the concentration had returned to its pre-bypass value.

An important consequence of hypotension and altered regional blood flow is the associated decrease in liver plasma flow as demonstrated by Koska, Romagnoli and Kramer (1981) using indocyanine green. Assuming that the clearance of indocyanine green is equal or closely related to liver plasma flow, they reported a 30% decrease in flow. This decrease in flow could increase the elimination half-life by decreasing hepatic clearance. Since the phenoperidine concentration appeared to be stable before cardiopulmonary bypass, the increase observed during bypass can be related to the decrease in hepatic flow. The decrease in liver flow may affect phenoperidine kinetics less than those of fentanyl, since the clearance of phenoperidine is greater than that of fentanyl (Fischler et al., 1985). This is probably the result of an extrahepatic elimination of phenoperidine by plasma and tissue esterases, which may induce a difference in behaviour during cardiopulmonary bypass.

The effects of hypothermia on liver function in animals appear similar to those of hypotension (Holley, Ponganis and Stanski, 1982). Decreases in hepatic extraction (Larsen, 1971) and metabolic clearance (McAlister et al., 1979) have been demonstrated during hypothermia; these may be the result of the temperature dependency of enzymatic activity or of marked intrahepatic redistribution of blood flow, or both.

During the period the lung is isolated from the systemic circulation, it may act as a reservoir for drugs—especially basic drugs. This has been demonstrated for fentanyl (Bentley, Cohanan and Cork, 1983). Thus, on the termination of bypass the washout of a significant mass of drug may increase the plasma concentration. Our data demonstrate that the phenoperidine concentration increases after termination of bypass, the infusion remaining constant. A 30% increase in fentanyl concentration was also observed after termination of the bypass (Koska, Romagnoli and Kramer, 1981).

Howie and colleagues (1982) have pointed out that the cardiopulmonary circuit can absorb fentanyl; they have demonstrated this fact on an *in vitro* model. It is doubtful whether this plays a major clinical role, since our data show an increase in phenoperidine concentration during cardiopulmonary bypass and identical concentrations

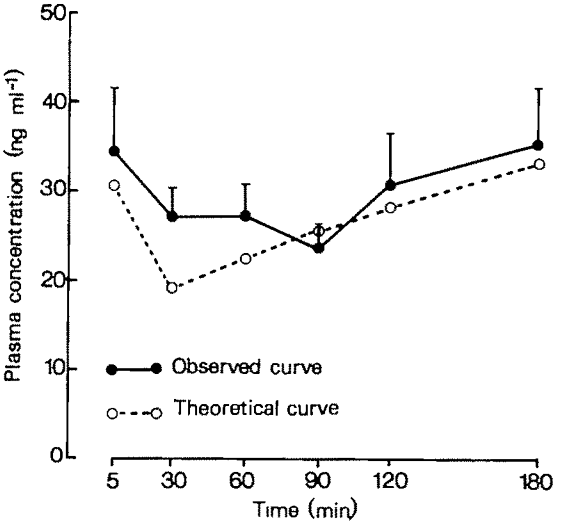

FIG. 3. Theoretical and observed (mean ± SEM) curves of phenoperidine concentrations. The theoretical curve has been calculated as the curve for the bolus dose plus the infusion one with the following formulae. Values are derived from an accompanying study on phenoperidine pharmacokinetics in anaesthetized patients submitted to general surgery and were corrected for the dose/ratio between both experiments (Fischler et al., 1985).

Theoretical curve for the bolus dose:

$$C_P(t) = 71.2e^{-0.309(t)} + 11.6e^{-0.0036(t)}$$

Theoretical curve for the infusion:

$$C_P(t) = \frac{k'_{01}}{V_1 . k_{10}} . (1 + \frac{\beta - k_{10}}{\alpha - \beta} \exp(-\alpha t) + \frac{k_{10} - \alpha}{\alpha - \beta} \exp(-\beta t))$$

where $k'_{01} = 5$ mg h^{-1} (83333 ng min^{-1}); $V_1 = 59701$ ml; $k_{10} = 0.0266$ min^{-1}; $\alpha = 0.309$ min^{-1}; $\beta = 0.0036$ min^{-1}.

were found from both venous and arterial limbs of the circuit.

Our data must also be discussed in the light of the results of the accompanying study on the pharmacokinetics of phenoperidine in anaesthetized patients undergoing general surgery (Fischler et al., 1985). Using the pharmacokinetic parameters which have been derived from that study, the phenoperidine concentration following a 5-mg bolus dose and a constant infusion of 5 mg h^{-1} could be calculated. Ninety-seven percent of the theoretical concentration at equilibrium, 55 ng ml^{-1}, would be achieved after 5 half-lives of elimination (950 min). The theoretical curve is displayed in figure 3, with the mean curve of the phenoperidine concentrations observed in the present study. The rates of change of the calculated and of the observed curves are similar. Observed results are always greater than the theoretical except for one point (90 min after the beginning of the phenoperidine administration); this difference can be accounted for by the large range of observed results or by the physiological consequences of the cardiopulmonary bypass.

No clinical evaluation of haemodynamic state can be undertaken because of the small numbers studied. However, if the anaesthetic regimen chosen is a form of balanced anaesthesia, this method of administration produces high plasma concentration of phenoperidine, even during cardiopulmonary bypass. Ideally, the infusion should be stopped earlier than in our study, possibly at the start of rewarming.

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PHARMACOKINETICS OF DIAZEPAM AND MIDAZOLAM WHEN USED FOR SEDATION FOLLOWING CARDIOPULMONARY BYPASS

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SUMMARY

The water-soluble benzodiazepine, midazolam, was compared with diazepam for postoperative sedation in patients following cardiopulmonary bypass. Midazolam in repeated doses produced a stable plasma concentration within 4 h, showed no tendency to cumulation and was cleared rapidly following discontinuation. Similar doses of diazepam given with the same frequency produced plasma concentrations which were still increasing at the time of discontinuation and which were still greater than their baseline values 24 h later.

Short-term ventilatory support is practised widely following open heart surgery (Lefemine and Harkin, 1966; Peters, Brium and Utley, 1979) and, for a variety of reasons, including a decrease in the incidence of psychiatric reactions (McClish, Andrew and Tetreault, 1968), its central neuromuscular blocking properties (Randall et al., 1961; Femi-Pearse, 1966), and the possible production of amnesia (Dundee and Pandit, 1972), diazepam is prescribed commonly to such patients. However, despite its obvious advantages, diazepam is by no means an ideal drug. It is not water-soluble, is associated with a high incidence of venous sequelae (Hegarty and Dundee, 1977) and, on account of its long half-life, has been shown to cumulate following multiple repeated doses (Gamble, Dundee and Gray, 1976). Moreover, this cumulation is further complicated by the hypnotic properties of the main metabolite—n-desmethyl diazepam.

The recent introduction of midazolam provides the clinician with a drug the pharmacokinetic profile of which more closely resembles the ideal for short-term multiple-dose usage. It has a short elimination half-life in relation to diazepam (Dundee et al., 1980; Smith, Eadie and Brophy, 1981) and is approximately one and a half times as potent as diazepam (Reves, Corssen and Holcomb, 1981). Its unique pH-dependent ring structure renders it reversibly water-soluble, a further advantage when compared with diazepam and, to date, no hypnotically active metabolites have been reported. In addition, midazolam has been shown to depress minimally the cardiovascular system (Kawar et al., 1983).

However, one cannot use pharmacokinetic indices derived from normal individuals to predict the behaviour of drugs in patients following the severe physiological upset of cardiopulmonary bypass. This paper reports the findings of a study in which the two drugs (diazepam and midazolam) were compared as sedative–hypnotics in the first 12–16 h following open-heart surgery carried out under cardiopulmonary bypass.

PATIENTS AND METHODS

The study was conducted in 19 patients following open heart surgery who had received no benzodiazepines in the 2 weeks before operation, and

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had no evidence of hepatic dysfunction on routine biochemical screening.

Anaesthesia comprised high-dose fentanyl (50 μg kg^{-1}), and nitrous oxide in oxygen. No benzodiazepines were administered during the intraoperative period. Pancuronium 0.1 mg kg^{-1} was administered to provide neuromuscular blockade.

Following anaesthesia the patients were randomly allocated to one of two groups. The first received diazepam 5 mg 2-hourly, the second midazolam 5 mg 2-hourly. Both drugs were given i.v. and supplemented with morphine 2 mg i.v. as required. Venous blood was drawn from both groups at 0, 7.5, 15, 30, 60 and 90 min and at 2, 4, 6, 8, 10 and 12 h after the initial dose, and the plasma concentrations of each benzodiazepine measured (gas–liquid chromatography) (Gamble et al., 1975; Howard et al., 1978). (The coefficient of variation of our analyses was 3.4% for diazepam, 9.8% for low concentrations of midazolam and 1.8% for high concentrations.) The latter samples were taken immediately before the next dose of benzodiazepine and so represent "trough" plasma concentrations. Thus we were able to study the distribution of the initial dose in detail over the first 2 h and to follow the cumulative effect of repeated doses.

As far as possible during the period of the study, the patients' blood volume, arterial pressure, temperature and acid–base status were kept constant and within their physiological ranges.

RESULTS

Table I shows that the two groups of patients were comparable in respect of average age, weight and duration of cardiopulmonary bypass. Both treatment regimens produced adequate sedation and all patients were successfully weaned from mechanical ventilation the morning after operation. The average time to discontinuation of the sedative drugs was 14.6 h in both groups. The mean dose of each benzodiazepine given was 41 mg.

The mean concentrations obtained following the initial dose are shown in figure 1. However, there were wide variations in the individual plasma concentrations of both drugs.

TABLE I. *Physical characteristics and duration of bypass in both groups of patients (average ± SEM)*

Drug	Age (yr)	Weight (kg)	Duration of bypass (min)
Midazolam	56±2.2	69±4.8	96±13.9
Diazepam	53±3.4	71±2.4	88±11.4

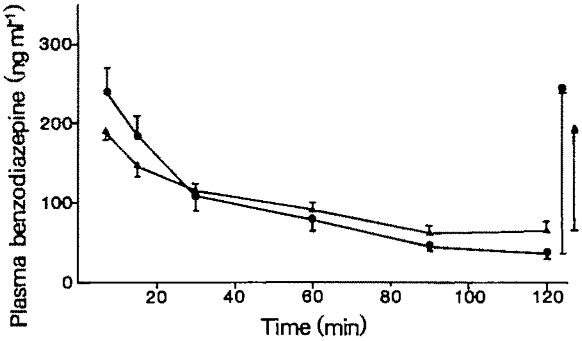

FIG. 1. Mean plasma concentrations (±SEM) over 2 h following an initial 5-mg dose of diazepam (▲) or midazolam (●). The bars at the right indicate the peak-to-trough variation for each drug.

There was a slight difference in the number of doses given to different patients, one in each series receiving seven doses and three in each receiving nine. However, this does not invalidate the main finding of the study which was the difference in mean plasma concentrations of the two drugs following repeat administration (fig. 2). After 4 h, midazolam trough concentrations became relatively stable, whereas plasma diazepam concentrations continued to increase throughout the period of administration.

Midazolam concentrations decreased to very low values within 6 h of discontinuation and by

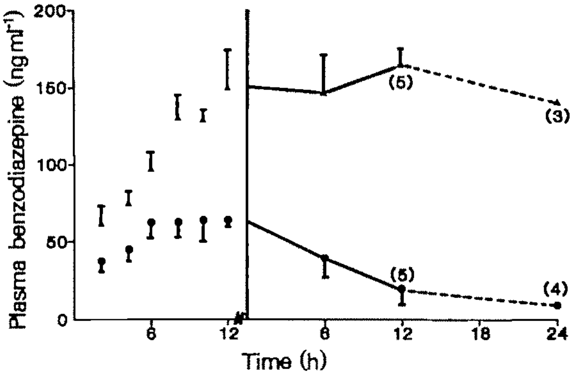

FIG. 2. Mean (±SEM) "trough" plasma concentrations over 12 h for diazepam (▲) and midazolam (●), following 5 mg i.v. 2-hourly. The plasma concentrations for 24 h following discontinuation are shown on the right. Ten patients received midazolam, and nine diazepam. At those times when samples were not available from every patient, the actual number is shown in parentheses.

24 h midazolam could not be detected in the plasma. In contrast, the plasma concentration of diazepam was still high 12 h after its discontinuation.

DISCUSSION

Previous work on the pharmacokinetics of midazolam has been limited to single-dose studies or studies during a steady-state infusion in volunteers. In healthy, young adults the elimination half-life ($T_{\frac{1}{2}}^{\beta}$) is 2–3 h. However, $T_{\frac{1}{2}}^{\beta}$ increases with age and, in clinical studies of midazolam as an induction agent, the nature of the operation has been shown to influence its elimination (Harper et al., 1985).

In a study of plasma diazepam and n-desmethyl diazepam concentrations following repeat doses of diazepam 10 mg 4-hourly given for periods of 6–22 days, Gamble, Dundee and Gray (1976) found that 6–10 days was required to reach a plateau. This is a reflection of the long elimination half-life of the drug and it is not surprising that we were unable to demonstrate any plateau in plasma diazepam concentration in the short periods used in this study. In contrast, despite the effects of age and surgery on $T_{\frac{1}{2}}^{\beta}$, the plasma concentration of midazolam stabilized within a short, clinically acceptable, period of time.

We have shown that, using an intermittent dose regimen, it is possible to obtain stable plasma concentrations. However, combining figures 1 and 2, it can be seen that the peak-to-trough variation was large with midazolam. This is unsatisfactory as it indicates a continual swing from very light to very deep sedation, resulting from a dose interval which was too long. After the first dose the average trough midazolam concentration was less than that considered necessary (Allonen, Ziegler and Kotz, 1981) for sedation (40 ng ml^{-1}), and it may be better initially to follow the first 5-mg dose with 2.5 mg every 1 h or to use an infusion. The initial dose and dosing interval used here had been chosen on the basis of previous practice with diazepam.

This study shows that midazolam offers distinct advantages over diazepam for the provision of sedation for short-term ventilation in a cardiac surgical intensive care unit. Despite the upset of cardiopulmonary bypass, the drug retains its short duration of action. In addition, the lack of cumulation means that adequate sedation can be assured for the immediate postoperative period without the risk of a prolonged hypnotic effect and that infusions of midazolam could be recommended for this group of patients.

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Br. J. Anaesth. (1985), 57, 886–891

CLINICAL ASSESSMENT AND PLASMA PHARMACOKINETICS ASSOCIATED WITH INTRAMUSCULAR OR EXTRADURAL ALFENTANIL

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SUMMARY

Patients with postoperative pain received alfentanil in doses of 15 μg kg^{-1} (n = 6) or 30 μg kg^{-1} (n = 6) via the extradural route or 15 μg kg^{-1} (n = 6) i.m. Effective analgesia was obtained in all patients in the extradural groups and in none in the i.m. group. Maximum pain relief developed within 10–15 min and the average duration of adequate analgesia was 78 min with the lower dose and 45 min with the higher dose, but this difference was not statistically significant. The 15-μg kg^{-1} extradural and i.m. groups showed the same pharmacokinetic pattern. Plasma concentrations were greater in the 30-μg kg^{-1} extradural group and this was associated with unwanted systemic effects. We conclude that the extradural administration of alfentanil can produce effective spinal analgesia. Its lipophilic property reduces the onset time, but does not modify its duration of action or impair absorption.

Extradural morphine is now used frequently in the postoperative period and produces effective analgesia of long duration. Nevertheless, side effects have been reported and have been related to the hydrophilic properties of the drug. Rapid systemic absorption may explain the early effects, and the persistence of morphine in the cerebrospinal fluid (CSF) the late respiratory depression (Chauvin et al., 1982; Kafer et al., 1983), the risk of which justifies prolonged and careful monitoring. The aim of this study was to determine whether alfentanil, a new opioid drug derived from fentanyl, could be used by the extradural route without side effects. Its physicochemical properties are quite different from those of morphine, alfentanil having a greater lipid solubility and a lower pK_a (Meuldermans, Hurkmans and Heykants, 1982). These properties could modify its speed of diffusion across the dura mater, its clearance from CSF and its binding to extradural lipids and, thus, modify the speed of onset, the duration of action, the plasma pharmacokinetics and the side effects of the drug.

PATIENTS AND METHODS

Eighteen patients, who were free from renal, cardiac and hepatic disease, gave informed consent for the study. They underwent orthopaedic, abdominal or vascular surgery and were studied at least 4 h after the operation. Patients were allocated randomly to one of three groups. The first group (group I, $n = 6$) received a single extradural injection of alfentanil 15 μg kg^{-1} diluted in 5% dextrose solution 5 ml. In the second group (group II, $n = 6$) patients were given alfentanil 30 μg kg^{-1}, again via the extradural route. In the third group (group III, $n = 6$) a single dose of alfentanil 15 μg kg^{-1} was injected i.m. Patients were studied during the next 4 h. Pain was scored on a scale from 0 to 5 (Samii, Chauvin and Viars, 1981) by an observer (M. C.) who was unaware of the method of analgesia. Heart rate, arterial pressure and respiratory rate were measured every 15 min. Side effects such as drowsiness, dizziness,

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pruritis and nausea, were noted. Arterial blood samples were withdrawn through a radial catheter before the injection of alfentanil and at 2, 5, 10, 15, 30, 60, 120, 180 and 240 min following administration, and blood-gas tensions measured. After centrifugation of the remainder of the blood plasma was stored at −25 °C until the determination of plasma alfentanil concentration by radioimmunoassay (Michiels, Hendricks and Heykants, 1983). The lowest limit of detection was of 0.1 ng ml^{-1} with an average coefficient of variation of 3.5 %. For each patient, the maximum plasma concentration ($C_{P\ max}$) and the time from administration to the maximum concentration (t_{max}) were determined. The apparent elimination half-life ($T_{\frac{1}{2}}$) was calculated by linear regression analysis of the log plasma concentration against time curve. Areas under the curves ($AUC_{0-\infty}$) were obtained using the trapezoïdal rule (Rowland and Tozer, 1980) and extending the integrated area from the last sampling point to infinity. The total clearance of the drug (Cl) was calculated from the formula:

$$Cl = \frac{\text{Dose}}{AUC_{0-\infty}}$$

Data were expressed as mean values ± SEM and statistical analysis performed using the t test to compare mean values of the kinetic parameters, the onset and duration of the analgesia and the side effects, and the Mann–Whitney test for pain intensity.

RESULTS

Basic patient data are listed in table I. Effective analgesia (pain score < 2) was obtained in all six patients in group II, in five of the six in group I, but in none of the patients in group III (figs 1, 2, 3). There was no difference in mean peak analgesic effect between groups I and II (table II). In both extradural groups the onset of pain relief was rapid although it occurred significantly ($P < 0.01$) earlier in group II than in group I (table II). The time to maximum analgesia did not differ between these two groups. The duration of action was short and there was no difference between groups I and II (table II).

TABLE I. *Clinical data (mean ± SD) in the patients studied*

	Group I	Group II	Group III
Age (yr)	49±12	46±10	40±17
Laparotomy	4	2	2
Thoracotomy	1	0	0
Orthopaedic	1	4	4
Mean pain intensity (scored 0–5)	4.1	3.8	3.8
Heart rate (beat min^{-1})	98±17	79±21	66±15
Mean arterial pressure (mm Hg)	87±17	88±11	84±6
Respiratory frequency (b.p.m.)	20±4	17±2	20±2
Pa_{CO_2} (kPa)	5.27±0.44	4.80±0.77	4.57±0.49

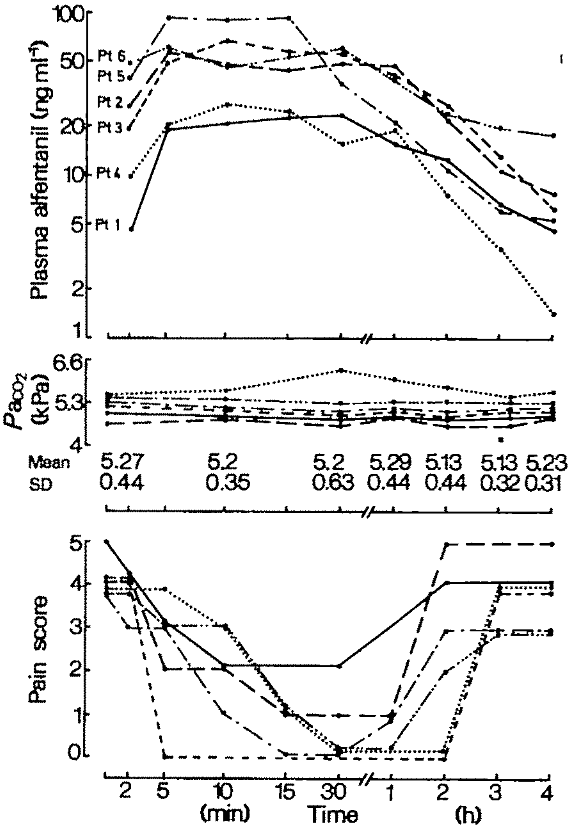

FIG. 1. Alfentanil plasma concentrations (upper panel); Pa_{CO_2} (middle panel); and pain score (lower panel) in patients in group I.

No patient in group III complained of or demonstrated any side effect and one patient in group I complained of pruritis. Variations in Pa_{CO_2} did not exceed 4 mm Hg in groups I and III. Side effects were frequent in group II (table III). These included drowsiness and dreaming (five patients); nausea (two patients), which was successfully treated by the administration of droperidol 2.5–5 mg i.v.; dizziness (one patient); cutaneous vasodilatation (three patients) and pruritis (two patients). There were no changes in heart rate and

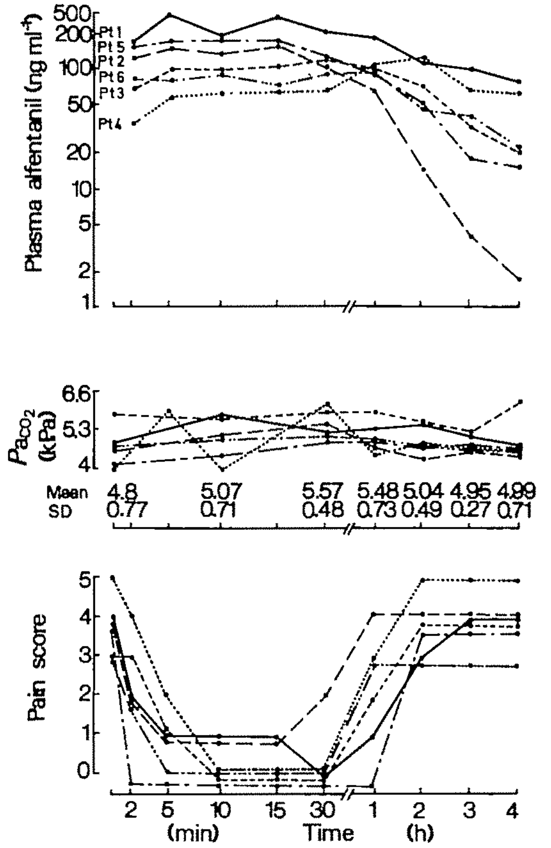

FIG. 2. Alfentanil plasma concentrations (upper panel); Pa_{CO_2} (middle panel); and pain score (lower panel) in patients in group II.

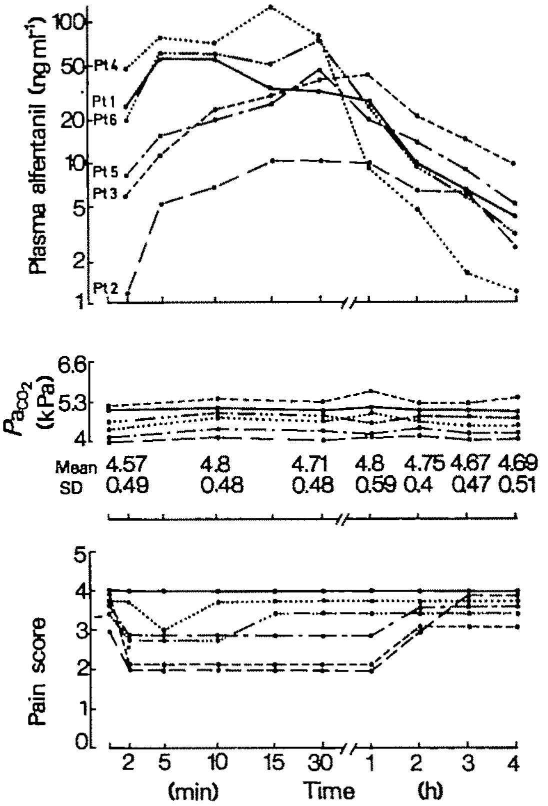

FIG. 3. Alfentanil plasma concentrations (upper panel); Pa_{CO_2} (middle panel); and pain score (lower panel) in patients in group III.

TABLE II. *Analgesia produced by the extradural administration of alfentanil*

	Group I	Group II	*P*
Mean maximum decrease in pain (scored 0–5)	3.7	3.7	ns
Onset of effective analgesia (min) (mean ± SEM)	12 ± 2	5 ± 1	< 0.01
Onset of maximum analgesia (min) (mean ± SEM)	17 ± 4	10 ± 4	ns
Duration of effective analgesia (min) (mean ± SEM)	78 ± 15	45 ± 10	ns

mean arterial pressure in any group. In group II (patients who received the higher dose of extradural alfentanil) significant respiratory depression (bradypnoea was of less than 10 b.p.m.) was observed in half of the patients. The onset of respiratory depression was very rapid, maximum changes occurring within 5 min (patients 2, 4) or 10 min (patient 5) of administration. One patient (No. 4) exhibited a marked decrease in respiratory rate (to 5 b.p.m.) with an increase in Pa_{CO_2} to 50 mm Hg. This depression was reversed immediately by naloxone 0.4 mg i.v., but analgesia persisted. Respiratory depression persisted for the duration of effective analgesia in the two other patients. Pa_{CO_2} did not increase because of verbal stimulation.

Figure 4 shows that mean plasma concentrations of alfentanil after the extradural or i.m. administration of alfentanil 15 µg kg⁻¹ did not differ. In these patients, absorption of alfentanil was very rapid after both i.m. and extradural injection. $C_{P\ max}$ was obtained within 16 min (table IV). Mean $C_{P\ max}$ and AUC were identical in groups I and III, and significantly higher in group II than in group I ($P < 0.02$). However, these values, when related to dose, were not significantly

TABLE III. *Number of patients experiencing side effects of the extradural administration of alfentanil*

	Group I	Group II
Drowsiness	0	5
Dizziness	0	1
Pruritis	1	2
Rash	0	3
Nausea	0	2

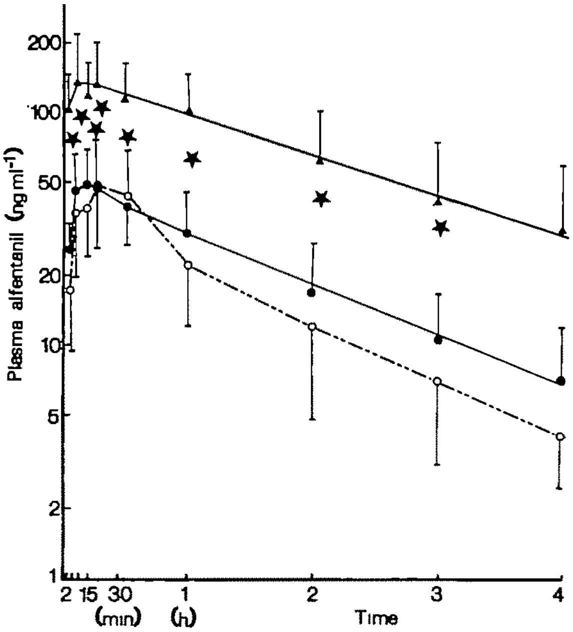

FIG. 4. Plasma concentrations of alfentanil after i.m. and extradural adminstration (mean ± SEM) in group I (●), group II (▲) and group III (○). *$P < 0.05$, group I *v.* group II.

TABLE IV. *Plasma pharmacokinetic parameters after i.m. and extradural administration of alfentanil (mean ± SEM)* *$P < 0.02$; **$P < 0.01$ (*group II* v. *group 1*)

	Group I	Group II	Group III
$C_{P\,max}$ (ng ml^{-1})	54.3±10.8	**155.2±28.0	74.2±18.4
t_{max} (min)	16±4	16±17	16±14
$AUC_{0-\infty}$ (mg litre^{-1} min^{-1})	6.4±1.3	*23.5±5.8	5.2±0.6
Cl (ml min^{-1} kg^{-1})	3.02±0.70	1.66±0.36	3.03±0.30
$T_{\frac{1}{2}}$ (min)	89.4±16.7	89.2±16.2	77.4±7.1

different. In group II mean alfentanil plasma concentration reached 100 ng ml^{-1} only 2 min after administration and remained above this value for 60 min. After 1 h, plasma concentrations decreased monoexponentially. The terminal half-lives ($T_{\frac{1}{2}}$) were similar in the three groups (table IV). The *Cl* of group II was lower than those of groups I and III, but this difference was not statistically significant. There was no correlation between analgesia or respiratory depression and plasma concentration in any group (figs 1, 2, 3).

DISCUSSION

Our results indicate that alfentanil 15 µg kg^{-1} i.m. does not produce adequate analgesia in the post-operative period, but that the extradural administration of the same dose does so, even though the increases in alfentanil plasma concentration were identical. This suggests that, like morphine (Weddel and Ritter, 1981; Chauvin et al., 1982), alfentanil has a direct spinal effect. Since plasma concentrations were similar after i.m. and extradural administration, it would seem that the drug is not retained by the extradural lipids, despite a lipid solubility 100 times greater than that of morphine (Kaufman, Semo and Koski, 1975). Lignocaine has a lipid solubility comparable to that of alfentanil (Tucker and Mather, 1979) and is known to be absorbed rapidly from the extradural space (Scott et al., 1972).

Increasing the alfentanil dose to 30 µg kg^{-1} produced both systemic and spinal effects (group II). Systemic side effects appeared in patients 2 and 5 soon after the extradural administration of alfentanil and patient 4 developed respiratory depression severe enough to necessitate the administration of naloxone. However, this patient had the smallest alfentanil concentrations in group II, with values identical to patients 2, 3 and 6 in group I. At the other extreme, patient 1 in group II had the highest plasma concentration of alfentanil, but no clinical evidence of respiratory depression. This lack of correlation between plasma concentrations and clinical effect has been described previously with fentanyl in man (Mather, 1983).

The lipophilic properties of alfentanil may account for its rapid onset of action, when compared with morphine. Rapid diffusion through the dura might produce an early peak in CSF concentration, as with pethidine (Tamsen et al., 1983). This very rapid onset is an interesting property of the drug which could be exploited in the operative period. The duration of action is short, but this cannot be a result only of its lipophilic properties, since other lipophilic opioids like fentanyl, pethidine (Torda and Pybus, 1982) and pentazocine (Kalia et al., 1983) have much longer durations when administered extradurally. Alfentanil dissociates rapidly from the μ opioïd receptors (Leysen, Gommeren and Niemegeers, 1983) and this could explain why it has a short duration of action.

Increasing the dose of extradural alfentanil did not increase the duration of action. With extradural morphine, a direct relationship between dose and both duration of effect and concentrations in CSF has been demonstrated (Nordberg et al., 1983). The lack of a dose-dependent duration of action with extradural alfentanil might be because the amount of the drug at the receptor in the spinal cord is not dose-dependent. This is in accordance with data which demonstrate that systemic absorption is dependent upon lipophilicity (Phillips et al., 1984). This greater systemic absorption of a lipophilic drug leaves a smaller quantity available for direct transfer across the dura.

The elimination half-life is the same as after i.v. administration. The clearances in our study are smaller than in other investigations (Bovill et al., 1982; Camu et al., 1982) which have reported the pharmacokinetic parameters of alfentanil after bolus injection of 50 and 125 μg kg^{-1} i.v. At both these doses, the values of V_D and *Cl* greatly exceeded those of the present study. However, the values of *Cl* reported here are in agreement with other studies (Bower and Hull, 1982; Hull, 1983) in which smaller doses were used. This is likely to be the result of the progressive decrease in the proportion bound to plasma protein with plasma concentrations greater than 100 ng ml^{-1} (Bower and Hull, 1982). We cannot explain the smaller *Cl* found with the higher dose in this study, except as a result of a small number of patients with marked individual variation.

In conclusion, effective analgesia of rapid onset can be produced by the extradural administration of alfentanil. The duration is short and this might be explained by rapid dissociation from the opiate receptor. Increasing the dose of extradural alfentanil did not result in increased duration of analgesia, but it did increase the plasma concentration. Thus, the lipid solubility of alfentanil did not impair its absorption from the extradural space and did not increase the proportion of the dose available for direct transfer across the dura.

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EXTRADURAL ANALGESIA IN THE MANAGEMENT OF SINGLETON BREECH DELIVERY

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SUMMARY

Ninety-four singleton vaginal breech deliveries conducted under extradural analgesia were compared with 277 singleton vaginal breech deliveries conducted without extradural analgesia. Mean duration of the first stage of labour was similar in both groups. Mean duration of the second stage of labour was prolonged and mean 1-min Apgar scores were less in fetuses weighing more than 2500 g in the extradural group. Mean 5-min Apgar scores, perinatal morbidity and maternal complications were similar in both groups.

Extradural analgesia may be advantageous in the conduct of vaginal breech delivery because pain is relieved, and the parturient is relaxed and co-operative. Relaxation of the pelvic floor may decrease the pressure on the fetal head and, by reducing the need for traction, decrease the likelihood of trauma to the fetus.

Surprisingly, many obstetricians are reluctant to use extradural analgesia in breech delivery because, since the first and second stages of labour are prolonged, more full breech extractions are necessary (Crawford, 1974). However, these observations were not confirmed in later studies (Donnai and Nicholas, 1975; Darby, Thornton and Hunter, 1976).

This study was undertaken to compare the duration of vaginal breech delivery and the fetal and maternal complications, with and without extradural analgesia.

PATIENTS AND METHODS

Five hundred and fifty-seven breech deliveries carried out between 1977 and 1981 have been reviewed. One hundred and eighty-six parturients who underwent Caesarean section were excluded from the study. Twins, stillborn fetuses, babies with congenital malformation and newborns weighing less than 1000 g were not included. Ninety-four (25%) vaginal breech deliveries conducted with extradural analgesia were compared with 277 (75%) vaginal breech deliveries conducted without extradural analgesia. Extradural analgesia was not performed whenever there was a history of trauma or operation on the vertebrae, in severely hypovolaemic or hypertensive parturients or whenever the anaesthetist was not available. Extradural analgesia was avoided in obstetric emergencies such as prolapse of cord, placental abruption or fetal distress (when the cause was not obvious). Previous history of migraine, headache, visual disturbances or surgery on the central nervous system were considered contraindications. Extradural analgesia was not performed whenever the parturient refused to give informed consent.

Parturients who received extradural analgesia were preloaded with a rapid infusion of lactated Ringer's solution 1000 ml, placed in a left lateral tilt and a continuous segmental (L2–4) extradural blockade was performed by the anaesthetist. Bupivacaine 0.25% in 10 ml was injected with the patient in a sitting position to provide analgesia in the second stage of labour. Extradural analgesia was performed when the parturient was in active labour with 3–4 cm cervical dilatation in multiparous women and 4–6 cm in primiparae, Maternal arterial pressure was monitored every 5–10 min.

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TABLE I. *Fetal birth weights in patients delivered with and without extradural analgesia*

Group	Fetal birthweight (g)	Extradural analgesia	Without extradural analgesia
I	1000–1499	1	17
II	1500–2499	7	44
III	2500–3499	67	172
IV	> 3500	19	44

Fetal heart rate monitoring and tocometry were performed in 71 (75%) of the parturients who received extradural analgesia and in 205 (74%) of the patients who did not. Women who delivered without extradural analgesia had local perineal infiltration with 1% lignocaine during the second stage of labour.

Twenty-eight (30%) parturients who received extradural analgesia and 89 (32%) parturients who did not receive extradural analgesia were primiparous. Medical and surgical induction of labour was performed in seven (7.4%) parturients who received extradural analgesia and in 23 (8.3%) who did not.

Parturients with and without extradural analgesia were divided into four fetal birthweight subgroups (table I). The durations of the first and second stages of labour, 1- and 5-min Apgar scores, maternal complications, perinatal morbidity and mortality were compared in both groups. The data were analysed with Pearson chi-square and Fisher exact tests.

RESULTS

Ninety-four singleton vaginal breech deliveries conducted under extradural analgesia were compared with 277 singleton vaginal breech deliveries conducted without extradural analgesia. Both groups were similar in regard to maternal age, parity, gestational age and frequency of frank, complete and incomplete breech-presented fetuses. Oxytocin augmentation of labour was performed in 53% of the parturients with extradural analgesia and in 36% of the women not receiving extradural analgesia. Pain relief was obtained in 76 (81%) parturients with extradural analgesia, 14 (15%) reported partial pain relief and four (4%) had no relief at all.

Ninety (96%) parturients who received extradural analgesia required an assisted breech delivery and four (4%) a full breech extraction.

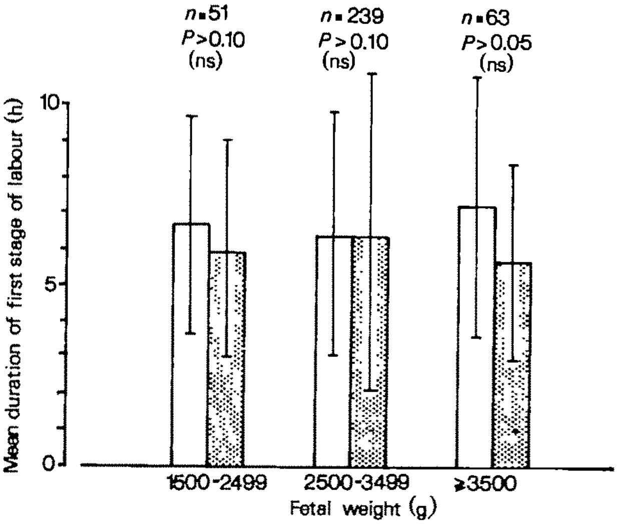

FIG. 1. Mean duration of the first stage of labour in singleton vaginal breech deliveries, conducted with (open columns) and without (stippling) extradural analgesia, divided into birthweight subgroups. Vertical bars represent ±1SD.

Assisted breech delivery was performed in 269 (97%) parturients without extradural analgesia and in nine (3%) full breech extraction was undertaken. General anaesthesia was used in two of the parturients without extradural analgesia to facilitate internal version and extraction because of fetal distress.

Mean durations of the first stage of labour in the different fetal birthweight subgroups, with and without extradural analgesia are presented in figure 1. No statistically significant differences were noted between the two main groups, and in the various birthweight subgroups. The mean duration of the second stage of labour is presented in figure 2. There were no statistically significant differences in the duration of the second stage of labour between parturients in subgroup II (1500–2499 g) who received extradural analgesia and those who did not. Parturients in subgroup III (2500–3499 g) and subgroup IV (more than 3500 g) who received extradural analgesia had a longer second stage of labour compared with those who did not receive extradural analgesia. The duration of the second stage of labour for parturients in subgroup IV with extradural analgesia was almost twice as long as in those who did not receive extradural analgesia. Fetuses in subgroup I were not analysed statistically because of the small numbers.

One- and 5-min Apgar scores from parturients

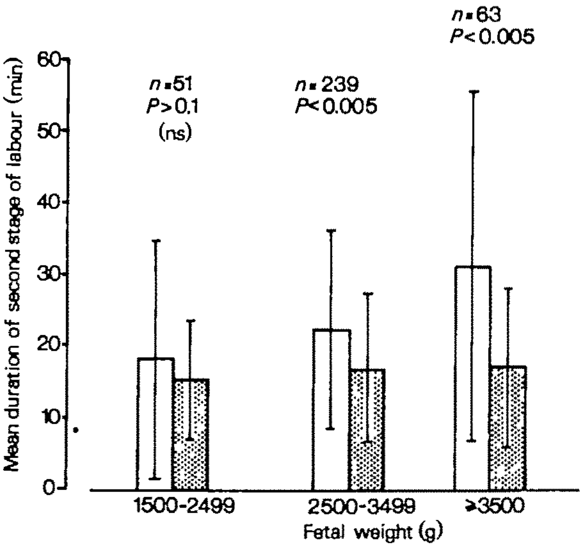

FIG. 2. Mean duration of the second stage of labour in singleton vaginal breech deliveries, conducted with (open columns) and without (stippling) extradural analgesia, divided into birth-weight subgroups. Vertical bars represent ±1SD.

who received extradural analgesia were compared with those from parturients who did not receive extradural analgesia (table II). Infants in birth-weight subgroups III and IV (more than 2500 g) of mothers who received extradural analgesia had lower 1-min Apgar scores compared with infants whose mothers did not receive extradural analgesia. Five-minute Apgar scores were similar in all birthweight subgroups with and without extradural analgesia.

Perinatal morbidity, such as neurological damage, respiratory distress, hyperbilirubinaemia, was similar in both groups ($P > 0.1$). One infant born to a mother who received extradural analgesia died on the 3rd day post partum because of cerebral haemorrhage. This infant was delivered using full breech extraction following prolapse of the umbilical cord. Two infants whose mothers did not receive extradural analgesia died: one because of prematurity with severe respiratory distress syndrome and the other from cerebral haemorrhage.

Maternal complications were similar in parturients with and without extradural analgesia. The only anaesthetic complications observed were transient hypotension in two (2%) parturients and a single case of uncomplicated dural puncture. Pathological fetal heart rate patterns were not observed in these three women and they had normal spontaneous assisted breech deliveries (5-min Apgar scores of 7, 8 and 10, respectively).

DISCUSSION

The optimum analgesia for breech delivery has been discussed widely. Earlier studies rejected extradural analgesia (Little and Friedman, 1958), while later studies advocated its use because of the good pain relief with relatively few adverse side effects (James et al., 1977; Hill et al., 1980). Improved techniques, anaesthetic agents and the advent of continuous extradural blockade together with minimal maternal and fetal complications made this analgesic method attractive in obstetrics (Rudick et al., 1983). However, there are adverse side effects which may compromize both mother and fetus. Maternal hypotension may cause changes in fetal Pa_{O_2} and produce abnormal effects on fetal heart rate (Willcourt, Paust and Queenan, 1982). Fetal acidosis is proportional to the severity of hypotension (Antoine and Young, 1982). In this series, only two patients had transient hypotension with no adverse effects. These complications can probably be prevented in most of the parturients by preloading with fluids, left lateral tilt and careful injection of a low dose of local anaesthetic agent.

The mean duration of the first stage of labour

TABLE II. *Depressed newborns with 1- and 5-min Apgar scores of less than 7, with and without extradural analgesia in four birthweight subgroups.* †*Fisher exact test*

Fetal wt (g)	1-min Apgar scores			5-min Apgar scores		
	Extradural	Non-extradural	P†	Extradural	Non-extradural	P†
1000–1499	1	11	> 0.5 (ns)	1	9	> 0.5 (ns)
1500–2499	2	12	> 0.5 (ns)	1	10	> 0.5 (ns)
2500–3499	11	1	< 0.05	2	1	> 0.1 (ns)
> 3500	5	0	< 0.01	1	0	> 0.1 (ns)

was similar in parturients who received extradural analgesia and in those who did not, although oxytocin was more frequently used in association with extradural analgesia (53% *v.* 36%). Similar results were reported by Rudick and co-workers (1983) with the vertex presentation. Extradural analgesia probably does not alter the normal progress of a well-established breech labour, a finding supported by Hill and colleagues (1980).

Crawford (1974) suggested that extradural analgesia prolonged the second stage of labour. Mean duration of the second stage of labour in our series was increased only in fetuses weighing more than 2500 g. It is possible that the delivery of a larger infant is slower and more maternal expulsive effort is needed. Abolition of the bearing down reflex may decrease maternal efforts and co-operation.

Hill and colleagues (1976, 1980) reported that breech fetuses delivered with extradural analgesia had higher pH values and the condition of the infant was even improved. In this series, 5-min Apgar scores and perinatal morbidity were not affected by extradural analgesia. However, 1-min Apgar scores were less in the larger infants whose mothers received extradural analgesia. The longer passage through the birth canal of the larger babies could have exposed some of them to partial or transient umbilical cord compression. It is possible that 1-min Apgar scores could be improved by the use of lower concentrations of bupivacaine in the second stage of labour. Decreasing the anaesthetic effect may improve maternal co-operation and shorten the second stage of labour. The significance of the lower 1-min Apgar scores must not be overemphasized, because they are of a little value in prediction of perinatal outcome. Furthermore, the number of full breech extractions was not increased in the parturients who received extradural analgesia.

In conclusion, we believe that extradural analgesia can be recommended in the management of vaginal breech delivery.

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EFFECT OF HALOTHANE ON SPINAL SOMATOSENSORY EVOKED POTENTIALS IN SHEEP

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SUMMARY

The effects of increasing concentrations of halothane on the morphology of spinal somatosensory evoked potentials (SEP) were studied in seven anaesthetized sheep. Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen. Ventilation was controlled throughout. Arterial pressure, temperature and end-tidal carbon dioxide tension were monitored. A lumbar laminectomy was performed, the sciatic nerve exposed and a baseline spinal SEP was recorded from the surface of the lumbar spinal cord. Halothane was introduced in incremental steps of 1% up to 3% and further SEP were recorded. These recordings revealed that the spinal SEP peak latencies and general waveform configuration were stable under halothane anaesthesia. Baseline SEP amplitude was similar to that obtained with 1% halothane; however, at concentrations of 2% halothane or greater, there was a significant ($P < 0.005$) attenuation of all components of the spinal SEP. These findings have important anaesthetic implications for patients undergoing spinal cord monitoring using SEP, although interspecies differences may occur.

The monitoring of spinal cord function by the intraoperative recording of somatosensory evoked potentials (SEP) to peripheral (lower limb) nerve stimulation has become common in spinal neurosurgery, and has generally superceded the "wake-up" test during orthopaedic surgery for scoliosis. Initially, reports described the use of cortical SEP as a guide to spinal cord integrity (Engler et al., 1978; Raudzens, 1982); however, problems occurred because of variable waveform morphology during the surgical procedure. Variables such as the anaesthetic agents, hypoxia, cerebral and spinal ischaemia and noise generated by surgical and monitoring devices complicated the acquisition and interpretation of the cortical SEP signal. Recording of spinal SEP has many advantages over the use of cortical SEP as a guide to spinal integrity (Bunch, Scarff and Trimble, 1983; Grundy, 1983; Jones et al., 1983). The spinal SEP can be easily and rapidly acquired, is of good amplitude and contains only short latency components, all of which facilitate intra-operative recording and its use as a specific index of spinal cord function.

The spinal SEP waveform can be attenuated by spinal cord hypoxia, ischaemia, compression and distraction (Nordwall et al., 1979; Bennett, 1983; Jones et al., 1983). There has, however, been no systematic study of the effect of particular anaesthetic agents on the spinal SEP waveforms. This is an important consideration during procedures such as Harrington instrumentation of the spine for scoliosis, since the inspired halothane concentration may be titrated to obtain a desired degree of arterial hypotension.

This report describes a study designed to examine and define the effects of varied inspired concentrations of halothane on the morphology of the spinal SEP waveforms. Changes in both peak

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latency and amplitude were studied in the lumbar region of the spinal cord.

MATERIALS AND METHODS

Seven adult cross-bred sheep were anaesthetized with thiopentone 8–10 mg kg^{-1}, a cuffed orotracheal tube was inserted, and neuromuscular blockade obtained with pancuronium 0.1 mg kg^{-1}. The lungs were ventilated with a pressure-cycled ventilator via a modified T-piece with 60% nitrous oxide in oxygen. Central venous access was secured via the external jugular vein and the femoral artery was cannulated to permit the continuous monitoring of the mean arterial pressure (Telectronics HS12-Medtel). The electrocardiogram was monitored via subcutaneous needle electrodes and the end-tidal carbon dioxide concentration recorded continuously (Datex CO2 analyser-CD300). Core temperature was monitored via a rectal thermistor probe.

The sciatic nerve was exposed in the thigh between the biceps femoris and semitendinosis muscles. A lumbar laminectomy was performed and the dura opened to expose the spinal cord.

Spinal SEP were generated by direct electrical stimulation of the sciatic nerve. Stimulation was applied through a stimulating unit consisting of parallel, curved blunt metal rods mounted in Perspex. Inter-electrode distance was 1.5 cm and the cathode was proximal to the anode. This unit was hooked beneath the segment of exposed sciatic nerve and electric shock stimulation, delivered as a square-wave pulse of 0.1 ms duration and 1–2 V amplitude, was applied via a stimulus isolation unit at a rate of 5 Hz. Stimulation voltage was constant throughout each experiment.

Spinal SEP were recorded directly from the spinal cord using a subdural platinum electrode referenced to a needle electrode in the adjacent para-spinal muscles. Signals were fed through a pre-amplifier (Medelec PA89) to a signal averaging unit (Medelec MS91). The frequency band was 20 Hz to 2 kHz. At least 120 events were averaged over epochs of 30–50 ms, although stable, reproducible waveforms were present after 30–40 events. Signals containing large amplitude interference were automatically rejected. SEP waveforms were reproduced on an oscilloscope where peak latency could be measured using a cursor with a digital readout. All recordings were duplicated and then printed on heat-sensitive paper. The details of this technique as applied to human spinal neurosurgery have been described previously (Whittle, Johnston and Besser, 1984).

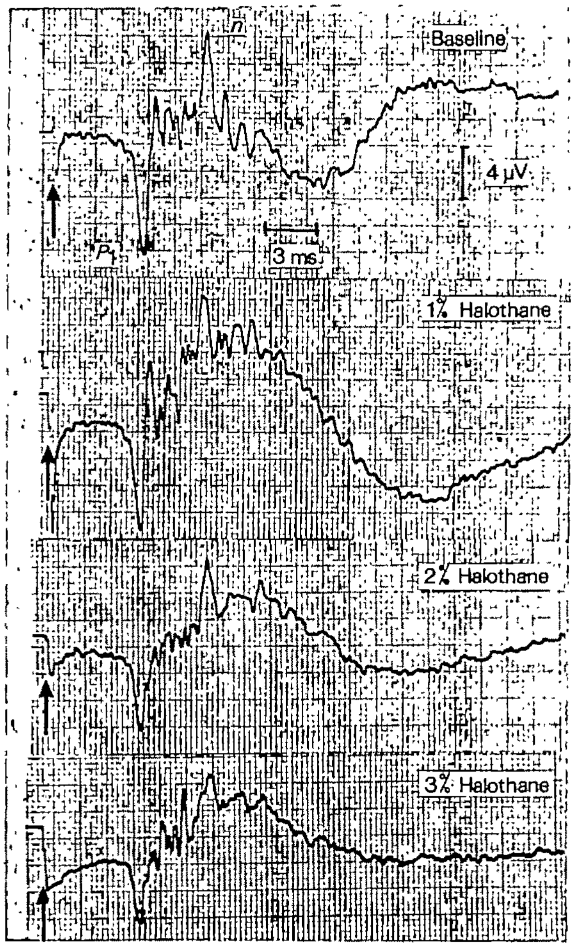

FIG. 1. SEP tracings at varying inspired halothane concentrations. The arrow indicates stimulus onset. P_1 is maximum positive deflection and n is maximum negative deflection.

Once a baseline SEP waveform had been obtained, halothane was introduced to the anaesthetic circuit from a recently calibrated vaporizer (Fluotec Mk2). Inspired halothane concentrations were sequentially increased by 1% each 30 min up to 3%. At the end of each 30-min period, inspired gas samples and end-tidal gas samples were taken for analysis (gas chromatography) to confirm that equilibration had occurred. Arterial pressure was maintained within physiological limits with an infusion of lactated Ringer's solution 10–20 ml kg^{-1} and, if necessary, an infusion of dopamine. Spinal SEP were recorded at the end of each 30-min period. Arterial pressure, heart

TABLE I. *Range of physiological variables in the seven sheep. MAP = mean arterial pressure*

Sheep No.	MAP (mm Hg)	End-tidal CO_2 (kPa)	Temperature (°C)
1	80.3–84.8	5.6–5.8	38.0–39.5
2	99.8–119.3	5.9–6.3	37.3–37.7
3	84.8–104.3	4.6–5.5	38.3–39.0
4	86.3–104.3	5.1–5.9	38.1–38.3
5	87.0–104.3	4.9–5.6	38.4–38.7
6	95.3–114.8	4.3–5.1	37.6–38.0
7	89.3–96.0	4.8–6.0	37.1–38.0

rate, core temperature and end-tidal carbon dioxide concentration were documented with each SEP recording.

When the effect of halothane on the amplitude of the spinal SEP was being quantified, the amplitude of the baseline recording from maximum positive deflection (P_1) to maximum negative deflection (n) was given an arbitrary value of 1.0 (fig. 1: upper trace). The amplitude of subsequent SEP obtained with varying concentrations of inspired halothane were calculated as a ratio of this baseline value.

RESULTS

A summary of the physiological variables measured in each sheep is shown in table I.

Gas chromatography confirmed that, in all instances, the end-tidal halothane concentration was greater than or equal to 87% of the inspired concentration.

Spinal SEP recordings were obtained from seven sheep (recordings at 2% and 3% halothane were not obtained in one sheep as a result of technical difficulties). Good amplitude (5–15 mV) spinal SEP were obtained in each animal. The waveform consisted of an initial positive wave (P_1), followed by a polyphasic segment of approximately 5 ms duration (fig. 1). The latency of the P wave and early polyphasic components were not altered (± 0.24 ms) by inspired halothane concentrations of up to 3% (fig. 1).

The amplitude of the waveform with 1% halothane was similar to baseline values (fig. 2). In several instances, however, 1% halothane appeared to augment the amplitude. At inspired halothane concentrations of 2% and 3% there was significant attenuation of the SEP amplitudes compared with the 1% values (paired t test, $P < 0.005$). The difference in amplitude of the waveform at halothane concentrations of 2% compared with that at 3% did not reach statistical significance.

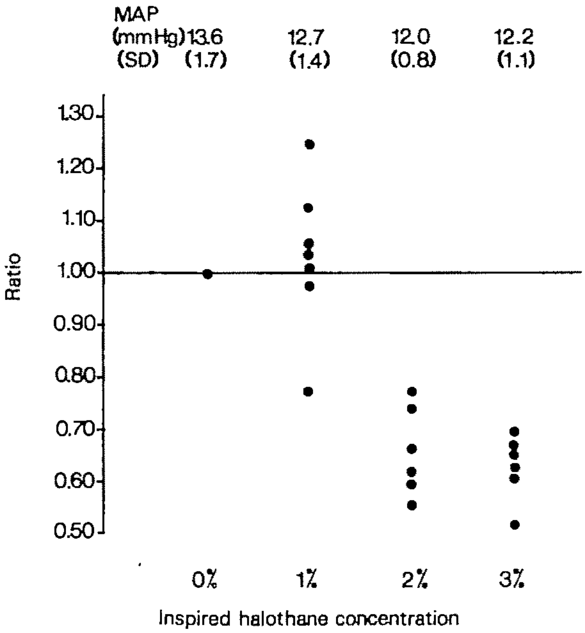

FIG. 2. Change in amplitude of SEP at varying halothane concentrations. Mean arterial pressure (MAP) and standard deviation (SD) are shown for each halothane concentration.

DISCUSSION

The successful use of evoked potentials to monitor the integrity of various afferent neural pathways during neurological or orthopaedic surgery depends upon accurate interpretation of changes in the evoked potential waveform. Since the work of Clark and Rosner (1973) on the effects of anaesthesia on evoked potentials, major advances have occurred in microprocessor based computer technology that have permitted the acquisition of evoked potential signals in increasingly more adverse recording conditions. These advances have necessitated a re-evaluation of the effect of anaesthetic agents on evoked potential waveform (Thornton et al., 1984).

A decrease in spinal SEP amplitude of greater than 10% monitored during scoliosis surgery has been noted in 30–34% of patients (Jones et al., 1983; Lamont, Watson and Green, 1983; Whittle et al., 1984). The cause of these random fluctuations is uncertain, since they frequently occurred independently of distortion of the vertebral column. Since high concentrations of halothane may have been used in these patients to facilitate therapeutic hypotension, it is possible that some of the attenuation in the spinal SEP was anaesthetic-induced. Indeed, results from our study suggest that halothane, administered at concentrations of 2% or greater, will significantly alter the amplitude of the spinal SEP. The changes in the physiological variables measured were deemed insufficient to alter spinal SEP morphology. However, peak latencies and the general configuration of the waveforms remain unaltered by halothane administered at equilibrated inspired concentrations of 3%.

The augmentation of the spinal SEP seen in some instances with 1% halothane may be the result of chemical de-afferentation of segmental spinal generators from inhibitory supra-segmental controls. Presumably, higher concentrations of halothane inhibit both supra-segmental and local spinal neuronal activity, causing attenuation of near-field signal potentials.

This finding of a decrease in SEP amplitude with inspired halothane concentrations of 2% or greater is at variance with the work of Nordwall and colleagues (1979) who noted no significant change in SEP amplitudes or peak latencies with up to 4% halothane in a cat model. This finding may be attributable to differences in their experimental programme. Thornton and colleagues (1984) showed attenuation of auditory evoked potentials with halothane anaesthesia. However, whether an analogy between the origin and properties of spinal cord field potentials and the effects of phamacological agents is comparable to brainstem auditory evoked potentials is contentious.

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INHALED ANAESTHETICS HAVE NO EFFECT ON FERTILITY IN *DROSOPHILA MELANOGASTER*

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SUMMARY

The potential effects of enflurane, isoflurane, halothane, fluroxene and nitrous oxide on mortality and fertility in Drosophila melanogaster *were examined. The* LD_{50} *value 1 day after exposure for 1 h was the same for males and females and was about 8% for enflurane, isoflurane and halothane, about 20% for fluroxene, and greater than 100% for nitrous oxide. Male and female fertility, however, were not affected by any of the anaesthetics, even at concentrations well above those used clinically.*

Epidemiological studies have led to the suggestion that an increased frequency of adverse reproductive effects may follow occupational exposure to waste anaesthetic gases. Spontaneous abortion among women directly exposed to anaesthetics and among wives of men exposed, and congenital anomalies among their offspring have been the focus of most studies (NIOSH, 1977; Ferstandig, 1978; Vessey, 1978; Baden and Rice, 1981). In addition, Knill-Jones and colleagues (1972) reported that the frequency of infertility among female operating suite personnel was twice as high as a comparable control group. Greater frequency of involuntary infertility among women in anaesthetic practice has also been reported by Tomlin (1979). In animals, the potential abortifacient and teratogenic effects of anaesthetic agents have been extensively studied. However, the effects of anaesthetics on fertility have not been systematically studied, even though there is limited evidence to suggest that these agents disrupt germ cells under certain conditions. Thus, the present study was undertaken to determine the effects of several anaesthetics on fertility under similar experimental conditions. The fruit fly, *Drosophila melanogaster*, a species widely used for genetic testing, was chosen as the test model.

MATERIALS AND METHODS

Two-day-old flies of a wild-type strain (Oregon R) of *Drosophila melanogaster* were used. All flies were reared in vials containing instant medium (Carolina Biological Supply, Burlington, NC). The cultures were maintained at a temperature of 25 ± 1 °C and a relative humidity of 50 ± 5%. The following anaesthetics were tested: enflurane, isoflurane, halothane, fluroxene and nitrous oxide. It was first necessary to establish the LD_{50} values for each agent so that appropriate concentrations could be chosen for the fertility tests. For enflurane, isoflurane and halothane, groups of 100 males and 100 females were exposed to 0, 0.5, 1, 2, 4, 6, 7, 8, or 16%. For fluroxene, two additional concentrations, 20 and 24% were used. For nitrous oxide, the concentrations were 0, 20, 40, 50, 60, 80 and 100%.

All exposures were for 1 h at 25 °C. During exposure, the concentration of oxygen was maintained between 19 and 23%, except for the 100% nitrous oxide group, for which it was 0%. The concentration of oxygen was monitored by an IL 402 Oxygen Monitor (Instrumental Laboratory, Lexington, Ma). Gas chromatographic measurements or infra-red gas analyses of anaesthetic concentrations were obtained at the beginning and end of exposure and showed that the concentration of the anaesthetics did not de-

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TABLE I. *LD_{50} (% v/v) values 24 h after an acute exposure of 1 h.* * *Values significantly greater than those observed with other anaesthetics.* ** *No deaths observed*

Anaesthetic	LD_{50} values Males	Females	Combined
Enflurane	8.96	8.13	8.70
Isoflurane	7.80	7.70	7.75
Halothane	7.29	8.03	7.65
Fluroxene	20.37*	20.69*	20.53*
Nitrous oxide	**	**	**

crease by more than 5 %. Following treatment, flies were returned to clean vials with fresh medium, and were counted 24 h later to determine the one day LD_{50} values using the probit analysis procedure. Fertility tests were performed at all concentrations up to and including 7 % for volatile agents and 100 % for nitrous oxide. No fertility tests were undertaken above 7 % for the volatile anaesthetics because concentrations greater than this percentage were lethal to 50 % or more of the fly population.

Immediately after counting, five males were selected at random from each treatment group. Each male was mated for 3 days to two untreated virgin females in individual vials with fresh medium. Males were then removed and immediately individually mated with two fresh females to produce the second brood. The mating procedure was repeated once more to produce the third brood. In addition, 10 treated virgin females were selected at random from each treatment group and allowed to mate in pairs with one untreated male; the same pattern of brooding was followed as for the treated males. The successive broods represent cells treated at different stages of spermatogenesis or at increasing times after oogenesis. The numbers of live male and female progeny produced for each brood were counted. The data were analysed using probit analysis and the Chi-square (χ^2) test. $P < 0.05$ was considered statistically significant.

RESULTS

From the percentage of flies dying at each dose over a 24-h period, the 1-day LD_{50} was calculated for each anaesthetic using probit analysis (table I).

TABLE II. *Total numbers of flies produced at each dose of each anaesthetic, regardless of broods*

Anaesthetic	Treated sex	Sex	Concentrations (% v/v) 0	0.5	1	2	4	6	7
Enflurane	M	M	614	581	628	612	558	664	628
		F	653	654	670	666	606	671	685
	F	M	700	708	621	639	641	640	682
		F	657	716	646	737	618	731	770
Isoflurane	M	M	753	752	670	697	728	752	628
		F	745	754	756	809	716	789	736
	F	M	748	764	790	684	863	749	634
		F	774	772	876	785	922	760	684
Halothane	M	M	554	516	644	555	545	489	602
		F	665	614	696	594	516	545	662
	F	M	626	578	613	641	692	529	667
		F	564	626	612	653	721	589	637
Fluroxene	M	M	716	677	646	668	644	636	652
		F	792	726	714	720	701	695	696
	F	M	663	639	646	643	609	636	638
		F	734	683	714	686	686	680	737
			Concentrations (% v/v) 0	20	40	50	60	80	100
Nitrous oxide	M	M	648	639	677	664	702	645	615
		F	729	742	823	731	730	721	649
	F	M	672	677	747	619	684	639	712
		F	727	754	791	714	763	718	744

Statistically, there were no differences in LD_{50} values for enflurane, isoflurane, and halothane with the values ranging between 7.29 and 8.96%. Values for fluroxene, however, were significantly greater than for the other anaesthetics ($P < 0.01$); an average dose of 20.5% of fluroxene was required for a one-day LD_{50}. Ninety-five percent or more of the flies succumbed within 24 h of treatment at a concentration of 16% for enflurane, isoflurane and halothane. Flies treated with fluroxene were more resistant: a concentration of 24% was required for 100% lethality. Interestingly, all flies exposed to 100% nitrous oxide survived, indicating that this species is extremely resistant to hypoxia.

There was no effect on fertility which could be related to treatment. That is, there were no significant differences of brood or total numbers of male and female offspring among the various treatment groups when data were analysed by χ^2 (table II).

DISCUSSION

Drosophila melanogaster was selected for this study because it is easily and economically reared and has a short generation time of about 10 days at 25 °C. Furthermore, next to man, its genetics and reproduction are best known. Thus, *Drosophila* has been used widely to study chemically-induced mutagenic and adverse reproductive effects. Infertility caused by drugs is one of the effects observed in this species (Dybas, Tyl and Geer, 1981; Nikki and Okada, 1981; Ranganath and Krishnamurthy, 1981; Brink, 1982). For example, Brink (1982) reported an increase in sterility when male and female adults as well as larvae of *Drosophila* were fed the pyrolozidine alkaloid, heliotrine. Moreover, an increased frequency of congenital anomalies in the abdomen of the fruit fly was noted. Such studies have led to the acceptance of *Drosophila* as a model for testing the general effects of drugs on fertility. Furthermore, use of the brooding technique in *Drosophila* enables determination of the specific stage of germ-cell development which is affected by a chemical.

Epidemiological studies have found an increased frequency of involuntary infertility in operating room personnel (Knill-Jones et al., 1972; Tomlin, 1979). However, many factors other than exposure to waste anaesthetic gases may have accounted for these findings. Several investigators have examined the effects of anaesthetics on fertility of rodents (Pope et al., 1978; Wharton et al., 1979; Wharton, Mazze and Wilson, 1981; Mazze et al., 1982) but results have been uniformly negative.

In addition to fertility studies, several attempts have been made to investigate the direct effects of anaesthetics on male and female germ cells in rodents. Atrophy of the seminiferous tubules, decreased sperm count and decreased testicular weight in rats exposed to nitrous oxide continuously or acutely have been reported (Kripke et al., 1976). Adverse effects were observed as early as 48 h after treatment was initiated, but were rapidly reversible when exposures ceased. Coate, Kapp and Lewis (1979) subjected rats to halothane 1 p.p.m. plus nitrous oxide 50 p.p.m., or to halothane 10 p.p.m. plus nitrous oxide 500 p.p.m. After 48 weeks of exposure, the frequency of chromosomal aberrations in spermatogonial cells from rats exposed to a mixture of nitrous oxide – halothane was significantly greater than from rats subjected only to air. However, the types of aberration noted probably were present too infrequently to cause decreased fertility and were not heritable. Land, Owen and Linde (1981) examined the sperm of mice exposed to various anaesthetics for 4 h per day, 5 days per week for 14 weeks. It was found that the percentages of abnormal sperm following exposure to 0.08% chloroform, 0.2% trichloroethylene or 1.0% enflurane were 3.5, 2.4, and 2.0%, respectively, which were slightly but significantly above the control value (1.4%). In contrast, Baden and colleagues (1980) observed a normal rate of abnormal sperm in Swiss/ICR mice exposed to 0.3% enflurane, 4 h per day, 5 days per week for 52 weeks. No increase in the rate of chromosomal aberrations in spermatogonial cells was noted. Overall, these studies indicate that anaesthetics have mild toxic effects on male germ cells which are, however, unlikely to be associated with infertility.

Most of these animal studies have been performed at different times, in different laboratories, under a variety of experimental conditions. Thus, it is difficult to obtain a consensus of absolute or relative risk among the agents. Our study is an attempt to examine several anaesthetics agents at one time under standard conditions in a well-validated model for infertility. Although not excluding the possibility that anaesthetics decrease fertility in man, our negative results in the fruit fly, together with those of others in rodents, must be regarded as encouraging for both operating room personnel and patients alike.

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ANAESTHESIA FOR MICROVASCULAR SURGERY

A Physiological Approach

D. J. F. MACDONALD

SUMMARY

The anaesthetic management of patients for microvascular free transfer surgery requires a sound knowledge of circulatory physiology. It is important to maintain adequate arterial pressure and cardiac output. Hypervolaemic haemodilution to a haematocrit of about 35% increases the cardiac output and improves flow in the micro-circulation. Systemic heat loss must be minimized and the transplant itself kept warm. Hypocapnia is to be avoided. Analgesia must be adequate. The degree of any induced vasodilatation must be balanced against the effect on the systemic arterial pressure. Measures instituted in theatre to produce optimum circulatory conditions must be maintained in the postoperative period.

The frequency of operations involving microsurgical anastomoses is increasing, and in many centres they are now considered routine (Jones, 1984). Conditions which can be more effectively treated include reconstruction following trauma or excision of malignant tumours, hypoplastic cosmetic defects, ununited fractures, radionecrotic ulcers and replantation of limbs or digits. In the West of Scotland Centre for Plastic Surgery the technique has been in use since 1974 and 213 elective operations had been performed by the end of 1984 (table I). It is anticipated that the benefits of these new techniques will become even more widely available as more surgeons take advantage of organized training courses, and as equipment becomes available in more hospitals.

Such operations can be time-consuming and even with increasing expertise and better selection of patients, the average duration is around 8 h in the West of Scotland. To the anaesthetist and other members of the theatre team who do not have access to the microscope, the operation may appear tedious, often with little systemic upset to disturb the conduct of anaesthesia. However, good anaesthetic management, based on a sound knowledge of circulatory physiology, is crucial to the success of the operation and the temptation to delegate it to the most junior members of the anaesthetic department must be resisted (Robins, 1983).

In most patients, blood vessels of 1–4 mm internal diameter are being anastomosed. Although they are relatively large in rheological terms (and in that sense "microvascular" is a misnomer), they come into the category of the resistance vessels and have a large amount of smooth muscle in their walls. Spasm of the vessel as a result of handling, cold stimulation or reflex activity may prejudice

TABLE I. *Number of elective operations for microvascular free tissue transfer performed in the West of Scotland Centre for Plastic Surgery, 1974–84*

Year	No. of operations
1974	1
1975	7
1976	11
1977	4
1978	9
1979	11
1980	17
1981	27
1982	36
1983	47
1984	43
Total	213

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the success of the operation. Such vessels chosen as recipients for the graft are usually sited peripherally and it can be assumed that they are subject to the reflexes which control skin and muscle blood flow. Where it is surgically feasible, the use of end-to-side anastomosis into larger vessels decreases the problem of reflex spasm. Vessels in the transplanted tissue are denervated, but are still subject to spasm as a result of physical and humoral influences.

PHYSIOLOGICAL CONSIDERATIONS

The interrelation of factors influencing the laminar flow of Newtonian fluids through rigid tubes is defined by the Poiseuille–Hagan formula:

$$\text{Flow} = (P_A - P_B) \times \frac{\pi}{8} \times \frac{1}{\eta} \times \frac{r^4}{L}$$

where $(P_A - P_B)$ = pressure difference between two ends of tube; η = viscosity; r = radius of tube; L = length of tube.

Although the circulation is too complex for a strict application of the formula, we see that changes in perfusion pressure, viscosity and cross-sectional area will all influence blood flow. The systemic arterial pressure is the major determinant of the pressure gradient across the transplanted tissue. In addition, since the blood vessels are distensible, the intraluminal pressure will of itself influence their diameter according to the Law of Laplace (fig. 1). The transmural pressure will be decreased if either the intravascular pressure decreases or the extravascular pressure increases (e.g. pressure from dressings, haematoma or oedema).

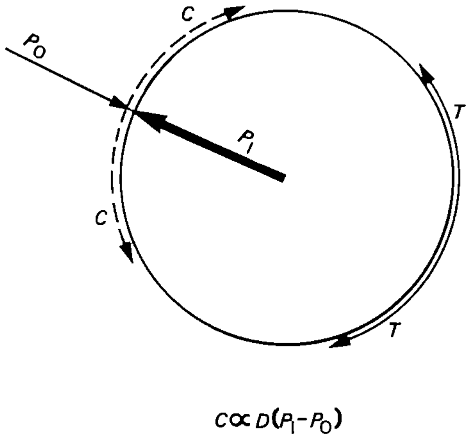

FIG. 1. *Law of Laplace*. Balance of forces in a distensible tube. T = Intramural tension tending to close vessel; C = circumferential component of transmural pressure $(P_I - P_O)$ which opposes T; D = diameter.

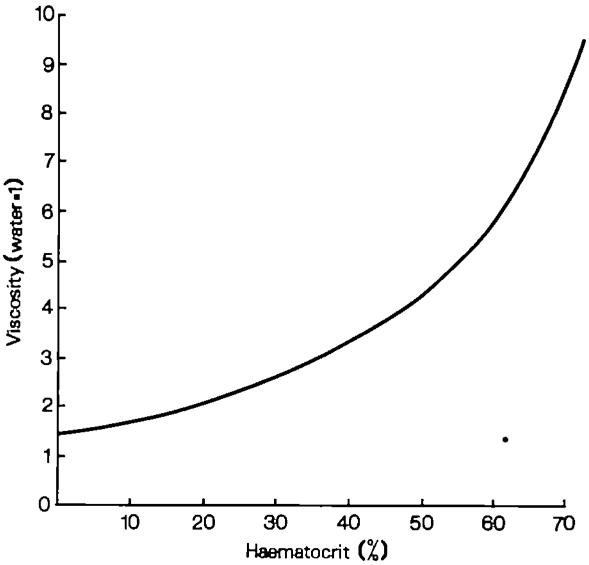

FIG. 2. Effect of haematocrit on viscosity. (Modified from A. C. Guyton's *Textbook of Medical Physiology*, 6th Edn, fig. 18.3, p. 207, with permission of the publisher, W. B. Saunders & Co.)

As flow is related to the fourth power of the radius, even a small change in cross-sectional area produces a large change in flow. In vessels with an internal diameter greater than 1.5 mm, the viscosity is closely related to the haematocrit (Guyton, 1981). This relationship is not linear and as the haematocrit increases above 40% the viscosity begins to increase dramatically (fig. 2).

Microcirculation

In the microcirculation of the flap itself, the same three principles of perfusion pressure, vessel diameter and viscosity apply. The blood viscosity, however, plays a relatively more important role. Blood is not a Newtonian fluid and its viscosity varies with conditions of flow. In very small blood vessels when flow is rapid, the cells line up with their discoidal surfaces facing each other and pass through in a column (Farhaeus and Lindquist, 1931). The effective viscosity under these conditions is that of the plasma surrounding the column of cells.

The pressure generating flow is known as the shear stress. In the microcirculation it can

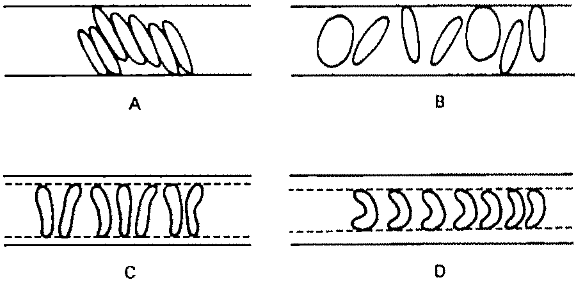

FIG. 3. Alignment of red cells in a capillary at increasing rates of flow. A: Stasis with rouleaux formation. B: Slow flow with cells evenly dispersed. C: Increasing flow leading to axial alignment of cells. D: Further increase in flow rate causing deformation of cells with increase in thickness of surrounding plasma layer (dotted lines). (Modified from R. L. Whitmore's (1968) *Rheology of the Circulation*, fig. 8.8, p. 127, with permission of the publishers, Pergamon Press Ltd, Oxford.)

decrease below normal values for a number of reasons, including a decrease in arterial pressure, an increase in venous pressure and an increase in the resistance to flow upstream as a result of vasoconstriction or increased whole blood viscosity. This decrease in shear stress is most likely to occur first at the level of the post-capillary venule (Schmid-Schonbein, 1981). Once it has occurred it will reduce the shear stress upstream and the process will extend into the capillaries. If the flow rate decreases below a critical value (fig. 3) the axial streaming of red cells does not occur and the cells are evenly distributed throughout the vessel. Thus, the viscosity increases in proportion to the haematocrit. Red cells may come into contact with the vessel wall and as the flow is further slowed they will then clump together in three-dimensional rouleaux which are much more rigid than individual cells and greatly increase the resistance to flow. Such rouleaux are reversible and will break up when exposed to increases in shear stress.

The tendency to rouleaux formation is also related to the concentration in the plasma of large molecules such as fibrinogen, and α2-macroglobulin. The infusion of colloid may have a similar effect; the tendency to promote aggregation is a function of concentration, molecular size and branching of the molecules and is, therefore, different for each colloidal preparation. Dextrans of molecular weight greater than 59000 predispose to the aggregation of red cells, whereas dextrans of lower molecular weight cause the break-up of such rouleaux (Thorsen and Hint, 1950). This is thought to be the result of dilution of the larger molecules and not a specific property of the low molecular weight dextran (Biro, 1980).

Metabolic autoregulation of regional blood flow can only function in the presence of an adequate perfusion pressure. Not all capillaries are perfused all the time, but because of varying tone in the pre-capillary sphincter they are alternately open and closed (Guyton, 1977). A good pulse pressure in the microcirculation ensures an effectively greater period of capillary patency for equivalent values of mean arterial pressure (Burton, 1954). It also improves the circulation of lymph and interstitial fluid. Cell metabolism is enhanced (Taylor, 1981). Arteriolar vasoconstriction produces a damping of the pressure wave and, in addition to a reduction in total flow, makes the flow less effective.

In planning anaesthesia, the aim must be to produce a hyperdynamic circulation with a high cardiac output, adequate vasodilatation and a large pulse pressure. This will not only ensure adequate microcirculatory perfusion of the transplanted tissue, but it should also minimize the risk of platelet deposition at the sites of anastomoses.

CONTROL OF ARTERIAL PRESSURE

An adequate arterial pressure with vasodilatation ensures good tissue perfusion by providing rapid regional blood flow, improving the patency of the microvasculature and maintaining the fluidity of the blood in the microcirculation. Of course one must balance the benefits of a hyperdynamic circulation against the need to provide good operating conditions and adequate haemostasis. In many operations, controlled hypotension may be indicated during the initial stages (e.g. excision of an extensive tumour or dissection of regional lymph nodes). In these patients, short-acting agents such as sodium nitroprusside or trimetaphan are to be recommended so that the arterial pressure can be restored quickly once the anastomosis has been completed, and adequate perfusion established rapidly. What constitutes an "adequate arterial pressure", of course, varies from patient to patient. In general, the author aims for a systolic arterial pressure of not less than 100 mm Hg. These considerations are highlighted in the following case report.

An 18-year-old woman had had a groin flap transplanted to her face. Systolic arterial pressure had been stable at 105 mm Hg and the skin of the flap was well perfused. While the skin edges were being sutured, the groin wound began to bleed, and about 150 ml of blood was lost fairly rapidly as a result of the slipping of a venous ligature. While this was receiving attention, the flap was noted to have turned grey and the systolic pressure to be 85 mm Hg. Rapid infusion of dextran 70 (250 ml) restored the arterial pressure to 105 mm Hg and the flap rapidly regained its original pink colour.

Unwise or uncontrolled decreases in systemic arterial pressure will bring the carotid sinus and aortic body reflexes into play and may also activate the renin–angiotensin and vasopressin systems with their intense vasoconstrictive effects. Fortunately, the effect of the baroreceptor reflexes is most marked on the splanchnic vessels and what vasoconstrictive action they have on skin and muscle blood vessels is overridden if there is concurrent stimulation of the low pressure receptors. Thus, a full vascular compartment allows better manipulation of arterial pressure. Naturally, it is important to have a reliable method of measuring the arterial pressure: in most patients one of the non-invasive automatic devices is satisfactory.

HYPERVOLAEMIC HAEMODILUTION

In patients with adequate cardiac reserve an increase in cardiac filling pressure to about 2 mm Hg greater than the control measurement will double the cardiac output and at the same time produce skin and muscle vasodilatation (Guyton, 1977; Abboud, 1979). These effects are partly a result of the intrinsic stretch mechanism and partly via the low pressure cardiopulmonary reflexes.

As the haematocrit is the most important determinant of viscosity in larger vessels and may affect shear stresses in the microcirculation, haemodilution produced by the infusion of blood volume expanders will further improve local tissue perfusion and may be of value provided it is not taken to the extent which would dangerously reduce oxygen transport. Conversely, an increase in haematocrit as a result of the injudicious transfusion of concentrated red cells will increase viscosity and decrease tissue perfusion.

Normovolaemic or hypervolaemic haemodilution has been shown clinically and experimentally to improve the chances of survival of tissues in which the circulation is compromised. Earle, Fratianne and Nunez (1974) demonstrated an improved survival of standard pedicle skin flaps in dogs which had been previously bled and had a haematocrit of 14–17% at the time of operation. In a retrospective study of diabetic patients undergoing amputations for peripheral vascular disease, Bailey and colleagues (1979) found that, in those patients whose wounds had healed satisfactorily by 1 month after operation, the preoperative haemoglobin concentration was lower than in the group which failed to heal. Schmid-Schonbein and Reiger (1981) treated 25 patients with skin lesions resulting from occlusive vascular disease by haemodilution to a haematocrit of 31% ± 2%. They achieved an improvement in skin blood flow and temperature with healing of lesions in the upper limb. The poorer healing of lower limb lesions was related to the number of demonstrated vascular blockages and the lower post-stenotic arterial pressure as measured at the ankle. The blood supply to ischaemic muscle has also been shown to be improved with normovolaemic haemodilution to a haematocrit of 35%, with consequent relief of intermittent claudication (Yates et al., 1979).

Although Gruber and Messmer (1977) considered a haematocrit of 30% to be optimal for the circulatory transport of oxygen, this has been challenged by Lundsgaard-Hansen (1980) who recommended that it should not be deliberately decreased to less than 35%. Any arterial hypoxaemia or myocardial depression which could occur during anaesthesia and surgery would carry a greater risk in the more anaemic patients.

As the management of patients having free-flap surgery should also include measures to promote active vasodilatation, there is no need to undertake any form of exchange transfusion. We must, however, consider what is the best fluid to administer to bring about this haemodilution and volume expansion.

Although Virgilio and colleagues (1979) demonstrated that it is possible to maintain an adequate circulating blood volume by replacing blood loss with concentrated red cells and electrolyte solution, even in a group of patients having an average intraoperative loss of 3.3 litre, they found it difficult to keep pace with the extravascular filtration of fluid. Animal experiments have shown that massive volume replacement with electrolyte solutions, although maintaining the circulating volume, leads to an increased mortality associated with peripheral oedema, severe acidaemia and low cardiac output (Takaori and Safar, 1967; Brinkmeyer et al., 1981; Dawidson et al., 1981).

Electrolyte solutions alone are ineffective in producing volume expansion and haemodilution and in fact may be detrimental to the survival of the flap by virtue of the oedema produced. Colloids, on the other hand, hold fluids in the vascular compartment and provide a more stable circulation (Takaori and Safar, 1967; Gruber, 1975; Messmer, 1975; Laks et al., 1976; Brinkmeyer et al., 1981; Dawidson et al., 1981; Shoemaker et al., 1981).

There is, of course, a danger of overloading the circulation, especially when left ventricular performance is already impaired (Virgilio et al., 1979). Infusions should be administered with caution, due cognisance being taken of the oncotic effect of the infusate (10% dextran 40, for example, has a volume effect approximately twice that of the actual volume infused). Central venous pressure monitoring should be routine and, in patients with known left ventricular inadequacy, measurement of the pulmonary capillary wedge pressure would be helpful although, in such instances, the patient's interests might be served best by a less ambitious although cosmetically less satisfying operative procedure.

There is no ideal blood volume expander, all solutions carrying a risk of anaphylactoid reactions. The risk is small (0.003–0.038%) compared with, for example, penicillin (1–5%) but such reactions are potentially lethal (Ring and Messmer, 1977). Dextran 40 has the added advantage of reducing the incidence of postoperative thrombo-embolic complications (Gruber, 1975).

It is the author's practice to commence an infusion of dextran 40 in 0.9% sodium chloride early in the operation at a rate which will maintain the central venous pressure about 2 mm Hg (2–3 cm H_2O) above baseline. Because of the instability of vasomotor tone immediately following the induction of anaesthesia, the first recorded measurement of central venous pressure should not necessarily be taken as "normal". Measurements should be taken several times during the first 30 min of anaesthesia before deciding what is the pressure to aim for. Because of its smaller molecular weght, dextran 40 does not remain in the circulation as long as other plasma substitutes, about half of it being lost from the circulation within 4 h of infusion. For this reason the infusion should be continued at a slower rate in the postoperative period. In most instances it works out that the patient receives 500–1000 ml during the operation and a further 500 ml over the next 12 h. Because available preparations of dextran 40 are hypertonic, they should be covered with an equal volume of Hartmann's solution to prevent extraction of fluid from the extravascular space. The bladder should be catheterized at the beginning of the operation in view of the anticipated duration of the operation, the volume of fluid to be infused and the diuretic effect of the dextran. Blood in the form of concentrated cells is given if the loss exceeds or shows a probability of exceeding 1 litre. Swab weighing and measurement of the suction is carried out, although it is recognized that this is somewhat inaccurate — especially in cases of such duration with deliberate blood volume expansion. Estimations of haematocrit at regular intervals during the operation, using a microcentrifuge in the theatre suite, have helped to achieve better control of fluid balance.

Robins (1983) abandoned the use of high molecular weight dextran because it caused excessive bleeding. This has not been our experience using dextran 40.

CONTROL OF CARBON DIOXIDE

Carbon dioxide causes depression of the myocardium and relaxation of vascular smooth muscle; however, the concomitant increase in sympathetic activity more than compensates for the cardiac effects. In anaesthetized patients the response is modified depending on the agents used and the degree of myocardial depression and sympathetic stimulation which they themselves produce. Even with halothane which produces minimal sympathetic activity, the sympathetic response to carbon dioxide is sufficient to overcome the direct myocardial depressant effect (Foëx, 1980).

The overall effects of an increase in carbon dioxide tension are increases in cardiac output, heart rate and arterial pressure, with a reduction in peripheral vascular resistance. Hypocapnia, on the other hand, causes an increase in peripheral vascular resistance and a decrease in cardiac output. Maintaining the carbon dioxide tension greater than its normal value would be an attractive way of producing optimum circulatory conditions for perfusion of the transplanted tissue, were we not concerned about the possibility of increased bleeding and the risk of cardiac irregularities — especially in the presence of certain anaesthetic agents such as halothane. However, it is important to avoid the hypocapnia which so easily occurs during controlled ventilation. An end-tidal carbon dioxide meter can be of great benefit in achieving the correct ventilation. If this equipment is not available, intermittent blood–gas analysis may be performed, but this requires arterial cannulation and has the further disadvantage that, unless the laboratory is adjacent to the operating theatre, there may be considerable delays in receiving the reports.

An anaesthetic technique using spontaneous respiration avoids the risk of hypocapnia. If used, it requires close monitoring to ensure that respiration does not become inadequate as a result of the central effect of anaesthetic and narcotic drugs, or the physical embarrassment of surgeon or assistant leaning on the patient. It also carries a greater risk of the patient coughing on the tube should the head be moved suddenly.

TEMPERATURE CONTROL

Under general anaesthesia, heat production and conservation are impaired, especially in the elderly and in infants. Twenty-year-old patients anaesthetized in an air conditioned operating room have been shown to suffer a decrease in body temperature of 0.3 °C per hour, whereas in 80-year-old patients in similar conditions the decrease was 1.1 °C per hour (Roe, 1970).

Surface radiation and evaporation are the main sources of heat loss during surgery. In addition, ventilation with dry gases at 10 litre min^{-1} removes about 40 kJ h^{-1} (Shanks, 1974); this is approximately 15% of an adult's total basal heat production. Cold infusion fluids will also tend to cool the patient, 1 litre of blood infused at 4 °C reducing the temperature of an adult patient by 1 °C (Roe, 1970). Other fluids, although stored at room temperature, will also tend to cool the patient if infused in larger quantities (Holdcroft, 1980).

In free tissue transfer surgery the flap is denervated and ischaemic. These are both factors which would predispose to vasodilatation, but the local decrease in skin temperature, which can occur from the time the flap is raised, leads to a proportionate reduction in blood flow (Awwad et al., 1983). This reduction in flow is probably the result of several factors: cold produces vasoconstriction, an increase in haematocrit, increased aggregation of red cells, and increased whole blood and plasma viscosity (Eiseman and Spencer, 1962; Schmid-Schonbein et al., 1973; Svanes, 1980; Harkness, 1981).

The direct vasoconstrictive effect of cold occurs even in denervated tissue (Keatinge, 1970). In addition to this local effect, there is an increase in vasomotor tone in response to cold stimulation of the skin or a decrease in temperature of the blood perfusing the vasomotor centre. These sympathetically-transmitted effects are decreased or abolished during anaesthesia, but become important during the recovery period. Therefore, steps should be taken to conserve heat from the commencement of anaesthesia and these should be continued during the recovery, transport and postoperative phases. The most important measure is to maintain the ambient temperature in the operating theatre. The recommended temperature is 24 °C, any increase above this being unpleasant for those working in the theatre and carrying a risk that the patient will develop hyperpyrexia (Clarke, Orkin and Rovenstine, 1954).

Although useful for infants, a warming mattress is not very effective in adult patients as only one-third of an individual's surface area is in contact with an under-mattress and the blood flow through this weight-bearing skin is probably impaired (Morris and Kumar, 1972). Used in conjunction with other measures here described, it may make a contribution to heat conservation and also to the care of skin pressure areas (see below).

The creation of a mini-environment by wrapping the patient in plastic sheeting effectively maintains body temperature (Dyde and Lunn, 1970). In survival situations it has been shown that simple polythene sheeting is as effective as the metallized variety (Marcus, Robertson and Langford, 1977). It is also cheaper and avoids any potential risk on the grounds of electrical safety. It does, of course, allow the build up of static electricity and should not be used in the presence of flammable anaesthetic agents. The use of plastic sheeting may be ineffectual in some operations because of the various areas which have to be exposed for surgical access. Many of the operations under discussion involve three different parts of the body — the main operation site, the donor area for the flap and the donor area for split skin.

It is also most important to keep the tissue flap warm throughout the procedure. This can be achieved fairly easily by using an appropriate operating light as a source of radiant heat and avoiding such practices as wrapping the flap in wet packs during dissection.

POSITIONING OF PATIENT

In view of the long duration of these operations and the often awkward position required for surgical access, extra care should be taken in positioning the patient at the beginning of the procedure.

The table mattress should be sufficiently resilient to prevent undue pressure on prominent parts. A ripple-type water mattress or fleecy under blanket should also be used. Limbs should be positioned and supported to avoid neurological damage or vascular compression. Pneumatic leggings should help to prevent the occurrence of deep venous thrombosis although, using hypervolaemic haemodilution as described above, we have not found this to be a problem.

CONTROL OF PAIN

Since pain and anxiety cause an increase in vasomotor tone it is important from the circulatory as well as the humanitarian point of view to relieve pain adequately both during and after the operation. In view of the duration of most of these operations, regional analgesia alone is not usually the best method of anaesthesia except in an emergency where an anaesthetic service is not available. Used in conjunction with basal sedation or light general anaesthesia, however, it has much to commend it as the profound analgesia and the sympathetic blockade are beneficial. The long action of bupivacaine makes it the drug of choice. Insertion of a catheter allows the administration of supplementary doses when the extradural, paravertebral or supraclavicular routes are used.

It is important not to add any vasoconstrictive drug to the local analgesic, as systemic absorption may lead to vasoconstriction in the vessels of the flap.

As the patient will be nursed in an intensive care environment, an alternative way to produce adequate analgesia is by the use of i.v. opiates, preferably given by continuous infusion.

VASODILATING DRUGS

Many drugs used in anaesthesia, including all of the volatile anaesthetic agents, have a vasodilating action which can be used to advantage. Isoflurane may prove to be the anaesthetic agent of choice as it produces a marked reduction in peripheral vascular resistance with minimal myocardial depression (Halsey, 1981).

Droperidol and some of the phenothiazine derivatives have mild α-adrenergic blocking activity. For a more reliable blockade Robins (1983) recommends the administration of thymoxamine from the time of premedication and for 7–14 days into the postoperative period.

Trimetaphan produces ganglion blockade, whilst nitroprusside and nitroglycerine have direct vasodilating actions on vascular smooth muscle. These are all powerful, short-acting hypotensive drugs and in the author's practice are seldom required. Nitroglycerine has a greater specificity for the venous side of the circulation. This property makes it valuable in the treatment of cardiac failure and ischaemic heart disease, but whether it confers any advantage in microvascular surgery is open to question, except in the patient with concomitant ischaemic heart disease.

Prostacycline offers exciting possibilities as it is a powerful direct-acting vasodilator which also inhibits platelet adhesion.

Papaverine can be used topically to treat vascular spasm, but has proved disappointing in our experience.

Shivering and vasoconstriction during emergence from anaesthesia can be controlled quickly using small boluses (5–10 mg i.v.) of promazine or chlorpromazine.

All of these drugs must be used with caution, the local benefits of vasodilatation being balanced against the tendency to cause systemic hypotension. Also, it must be remembered that the greater the skin vasodilatation produced, the greater will be the heat loss unless adequate measures are taken to prevent it.

CONCLUSION

There are many different ways of achieving the desirable circulatory conditions discussed. Choice of anaesthetic techniques and agents will depend on the medical condition of the patient, the nature and site of the defect being reconstructed and the anaesthetist's personal preference.

Regional variation in circulatory reflexes and the dominance of some reflexes over others can be manipulated to advantage. For example, a high central venous pressure produces skin and muscle vasodilatation via the low pressure baroreceptors which override the vasoconstrictive response to arterial hypotension, to chemoreceptor stimulation and to somatic afferent stimulation (Abboud, 1979). In addition, it causes an increase in cardiac sympathetic discharge and a reduced renal sympathetic discharge, leading to an increase in heart rate and a relative diuresis (Linden, 1979). Direct and reflex stimulation of the vasomotor centre by heat override the vasoconstrictive reflexes resulting from pain or hypotension (Abboud, 1979) and chemoreceptor stimulation by carbon dioxide produces skin vasodilatation while at the same time increasing the arterial pressure by reflex splanchnic vasoconstriction and a sympathetically-mediated increase in cardiac output (Reitan, 1982).

Even when the operation has been successfully completed and the circulation to the transplanted tissue established, its survival is still precarious. The period of initial recovery from the anaesthetic is one when the patient's cardiovascular state is particularly labile, and it does not take much to initiate the vicious cycle of microvascular stasis and eventual thrombosis at the sites of anastomoses.

With the passing of time, the risk of losing the flap diminishes, but the patient must be supervised carefully for the first 48 h following surgery. Central venous pressure monitoring and fluid replacement must be continued; the patient must be kept warm and analgesia must be adequate.

This paper has given a personal approach, developed over a number of years, to the problems of anaesthesia for microvascular surgery. There would be great difficulty in proving the value of any individual measure. Many other factors such as the age of the patient, the state of health of the vasculature, the technical problems of the operation and the skill of the operator also determine the success or otherwise of the operation.

The philosophy described has led to an anaesthetic technique satisfactory to both the anaesthetist and the surgeon. It is presented here in the hope that it will be of some assistance to colleagues as they plan the anaesthetic management of such patients.

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LABORATORY EVALUATION OF LOW-PRESSURE TRACHEAL TUBE CUFFS: LARGE-VOLUME *V.* LOW-VOLUME

J. M. KIM, J. V. MANGOLD AND D. C. HACKER

SUMMARY

Large- and low-volume low-pressure tracheal tube cuffs were compared during exposure to nitrous oxide. The compliance of both types of cuff when measured inside and outside an artificial rigid trachea, the volume of intubated cuff, the residual volume, the nitrous oxide diffusion time, and the specific diffusion rate of the cuff membrane to nitrous oxide were measured in the laboratory. From these variables, the diffusion rate of nitrous oxide, the surface area available for nitrous oxide diffusion, the tracheal wall pressure exerted by cuff, and the degree of folding of the intubated cuff were derived. The results showed that the rapid increase in pressure of the large-volume cuff when intubated was caused by low compliance, the large surface area available for nitrous oxide diffusion, and the considerable permeability of the cuff membrane to nitrous oxide.

Intubation of the trachea with large-volume, low-pressure cuffed tubes provides a tracheal seal at low cuff pressure and is claimed to decrease the possibility of tracheal injury. However, if nitrous oxide is administered, it will diffuse into the air-inflated cuff faster than nitrogen diffuses out, with a consequent increase in cuff pressure (Stanley, Kawamura and Graves, 1974). Moreover, the increase in cuff pressure has been shown to be more rapid in low- than in high-pressure cuffs, the cuff pressure being occasionally as high as 200 mm Hg in low-pressure cuffs (Stanley, 1975). It was reported (Kim, 1980) that the cuff pressure of an air-inflated American HiLo Tracheal Tube increased more rapidly than that of the Shiley Low Pressure Endotracheal Tube when both were exposed to nitrous oxide during clinical anaesthesia. A subsequent study on these two tracheal tubes by other investigators (Kosanin and Maroof, 1981) confirmed this finding.

The present laboratory investigation was conducted to elucidate the factors which may contribute to the more rapid increase in cuff pressure in the large-volume cuffed American HiLo Tracheal Tube. The Intermediate hilo Tracheal Tube was included for comparison.

MATERIALS AND METHODS

Three types of low-pressure cuffed tracheal tubes (10 each) of the same internal diameter (7.0 mm) were studied. The American HiLo tracheal tube (HiLo) represented the large volume, the Intermediate hilo tracheal tube (Inter hilo) the intermediate volume, and the Shiley Low-Pressure endotracheal tube (Shiley) the low-volume cuff. The mock trachea used in the experiment was a 20-ml glass syringe barrel with internal diameter of 20 mm.

To evaluate the performances of each type of cuff, duplicate measurements of the following variables were made using the techniques described.

Compliance of non-intubated cuff (ml/20 cm H_2O). The volume of air released from the non-intubated (i.e. when not in mock trachea) cuff when the cuff pressure was decreased from 40 to 20 cm H_2O. The method of adjusting the different

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cuff pressures and measuring volumes is illustrated in detail in figure 1.

Compliance of the intubated cuff (ml/20 cm H_2O). The volume of air released from the intubated cuff when the cuff pressure was decreased from 40 to 20 cm H_2O. The same apparatus and techniques were used as above, except that the tracheal tube was placed in the mock trachea.

Volume of intubated cuff (ml). Following the conclusion of the measurement of compliance of intubated cuff, the volume of the intubated cuff at a cuff pressure of 20 cm H_2O, was measured by aspirating the cuff air into a well-lubricated glass syringe.

Residual volume (ml). After the pressure in the non-intubated cuff was adjusted to 2 cm H_2O using the technique described in figure 1, the cuff volume was measured by aspiration.

Diffusion time (min/20 cm H_2O). The time required to increase the pressure in the intubated cuff from 20 to 40 cm H_2O when 100% nitrous oxide was introduced around the intubated cuff (the technique is described in figure 2).

Specific diffusion rate (ml cm^{-2} min^{-1}). The volume of nitrous oxide which diffused through the 1-cm^2 area of cuff membrane when the area was insufflated with 100% nitrous oxide for 1 min. The technique described in figure 3 measured the volume of nitrous oxide which diffused through the 3.14-cm^2 area of cuff membrane over 1 h (ml/3.14 cm^2 h^{-1}). From the measured value, the specific diffusion rate was calculated.

From these measured variables, *diffusion rate* (volume of nitrous oxide diffused into intubated

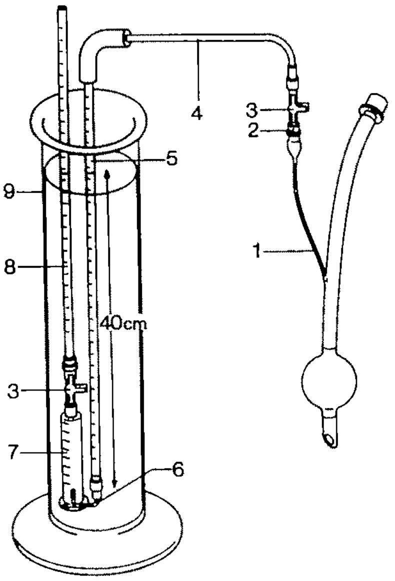

FIG. 1. Apparatus designed to adjust cuff pressures and measure volumes. The cuff was inflated with air to exceed an estimated cuff pressure of 40 cm H_2O. The inflation valve (2) of the cuff catheter (1) was opened to a central venous pressure manometer (CVPM) (5), the distal opening of which was located 40 cm under the water surface. This manoeuvre equilibrated cuff pressure to 40 cm H_2O after excess cuff air bubbled out through the distal opening of the CVPM. The cuff pressure, 40 cm H_2O, was then decreased to 20 cm H_2O by increasing CVPM from 40 to 20 cm under the water surface. As the cuff pressure was decreased, excess cuff air passed through the needle hook (6) and was trapped in the collecting syringe barrel (7) which had been prefilled with water. The volume of the trapped air was measured after the air–fluid level in the collecting syringe barrel was brought to match the water surface in the reservoir (9). (3) = Three-way stop-cock; (4) i.v. extension tubing; (8) = handle (second CVPM).

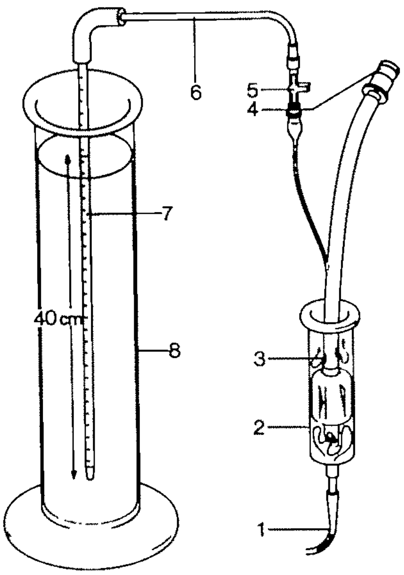

FIG. 2. Apparatus designed to measure the diffusion time. The proximal opening of tracheal tube was plugged with a rubber stopper (4), and two side holes were punched out just above the cuff (3). The tracheal tube was placed in the mock trachea (glass syringe barrel, 20 ml, 2 cm i.d.) (2), and the cuff inflated with air through the three-way stop-cock (5) until the water column in the lumen of the CVPM (7) descended to 20 cm under the water surface to achieve a cuff pressure of 20 cm H_2O. Nitrous oxide 100%, 3 litre min^{-1}, was delivered into the mock trachea through the gas inlet (1) (arrows indicate the pathways of nitrous oxide). Both proximal and distal surfaces of cuff membrane were insufflated by nitrous oxide. As the cuff pressure increased, the water column of the CVPM continued to descend until a meniscus was formed at the distal opening of the CVPM when the cuff pressure reached 40 cm H_2O. The time interval between the initiation of nitrous oxide delivery and the meniscus formation was regarded as the diffusion time. (6) = i.v. extension tubing; (8) = water reservoir.

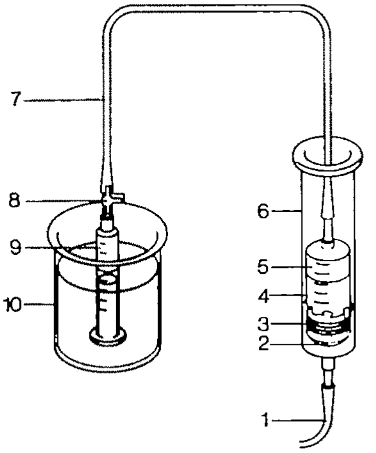

FIG. 3. Apparatus designed to measure the specific diffusion rate. A syringe barrel (20 ml, 2 cm i.d.) was transsected at the 10-ml marking (5). The calculated area of the open end of transsection (2 cm i.d.) was 3.14 cm^2. A double folded Latex Tubing (Penrose) (flat size, 1.25″ and diameter, 0.75″) (4) was wrapped around the outer wall of the transsected syringe barrel as padding. The transsected open end was covered with a cut piece of cuff membrane (2) using a rubber band (3). An air-tight seal between the transsected open end and covered cuff membrane was confirmed by pressurizing the syringe barrel with air under the water. The apparatus was then assembled as shown. The area of cuff membrane covering the transsected open end (3.14 cm^2) was insufflated with 100% nitrous oxide 3 litre min^{-1}; delivered through the gas inlet (1) for 1 h. The expanded volume of air was transferred via i.v. extension tubing (7) into the submerged collecting syringe barrel, 3 ml (9) which was prefilled with water. The volume of air trapped in the collecting syringe barrel was measured at the end of 1 h in a manner previously described. (6) = Syringe barrel, 50 ml; (8) = three-way stop-cock; (10) = water reservoir.

cuff in 1 min), *surface area* (area of intubated cuff available for nitrous oxide diffusion), P_{tw} (tracheal wall pressure exerted by the intubated cuff), and *degree of folding* of intubated cuff membrane were derived by the following equations:

Diffusion rate (ml min^{-1}) =

$$\frac{\text{compliance of intubated cuff (ml/20 cm } H_2O)}{\text{diffusion time (min/20 cm } H_2O)}$$

Surface area available for nitrous oxide diffusion consisted of two areas, the free area (area not in contact with the "tracheal" wall where nitrous oxide contacts freely), and the channelled area (area created by folding of cuff membrane through which nitrous oxide channelling occurs):

Surface area (cm^2) =

$$\frac{\text{diffusion rate (ml min}^{-1})}{\text{specific diffusion rate (ml cm}^{-2}\text{ min}^{-1})}$$

Tracheal wall pressure could be calculated from the difference in cuff compliance inside and outside the trachea (Homi et al., 1978):

$$P_{tw} \text{ (cm } H_2O) = P_{int} - P_{non\text{-}int}$$

P_{int} = pressure of intubated cuff for the given volume of cuff air; $P_{non\text{-}int}$ pressure of non-intubated cuff for the given volume of cuff air.

In our investigations, the values of P_{int} were derived from the pressure values obtained from the intubated cuff. The values of the $P_{non\text{-}int}$ can be estimated by comparing the value of the volume of intubated cuff with the value of the residual volume. For example, if the value of the volume of intubated cuff is smaller than the value of the residual volume, the value of $P_{non\text{-}int}$ will be negligible (less than 2 cm H_2O); therefore, the P_{tw} will be equal to or less than 2 cm H_2O smaller than the indicated cuff pressure. If the value of the volume of intubated cuff is larger than the value of the residual volume, the value of the $P_{non\text{-}int}$ will be significant (more than 2 cm H_2O); therefore, the discrepancy between the P_{tw} and the indicated cuff pressure will be more than 2 cm H_2O.

Degree of folding. When the large-volume, floppy cuff is inflated in the "trachea", the cuff membrane will fold. The degree of folding relates volume difference between the residual volume and the volume of intubated cuff:

degree of folding $\propto$

(residual volume − volume of intubated cuff)

In other words, if $P_{tw} = P_{int}$, the cuff folds. If $P_{tw} < P_{int}$, the cuff does not fold.

RESULTS

The measured and derived variables for the three types of low-pressure tracheal tube cuffs are summarized in tables I and II; the characteristics of each are described below.

American HiLo Tracheal Tube cuff

When the cuff was inflated outside the "trachea", the compliance was higher than that of the other two tubes. However, once the cuff was inserted to the rigid mock trachea, the compliance decreased substantially. Since the volume of intubated cuff was much less than residual volume, all of the cuff pressure was transmitted to the tracheal wall and the degree of folding should be marked. The short diffusion time was the result of a rapid specific diffusion rate, a high degree of folding and a low compliance of intubated cuff.

TABLE I. *Measured variables of three types of low-pressure tracheal tube cuffs (mean ± SD)*

	Compliance		Intubated cuff vol. (ml)	Residual volume (ml)	Diffusion time (min/20 cm H_2O)	Specific diffusion rate (ml cm^{-2} min^{-1})
	Non-intubated (ml/20 cm H_2O)	Intubated (ml/20 cm H_2O)				
HiLo	2.5±0.1	0.3±0.1	8.9±0.2	16.7±1.0	7.8±1.2	1.25±0.05
Inter hilo	1.9±0.1	0.3±0.1	7.2±0.1	11.9±0.2	11.1±0.5	—
Shiley	1.8±0.1	0.7±0.1	8.5±0.2	7.6±0.7	23.6±1.3	0.84±0.05

TABLE II. *Derived variables of three types of low-pressure tracheal tube cuffs.* P_{tw} = *tracheal wall pressure;* P_{int} = *intubated cuff pressure;* $P_{non\text{-}int}$ = *non-intubated cuff pressure. Diffusion rate = compliance of intubated cuff/diffusion time; surface area = diffusion rate/specific diffusion rate;* $P_{tw} = P_{int} - P_{non\text{-}int}$; *degree of folding* ∝ *residual volume − volume of intubated cuff*

	Diffusion rate (ml min^{-1})	Surface area (cm^2)	P_{tw} (cm H_2O)	Degree of folding
HiLo	0.039	5.82	$P_{tw} = P_{int}$	Marked
Inter hilo	0.027	4.03	$P_{tw} = P_{int}$	Minimum
Shiley	0.030	6.82	$P_{tw} < P_{int}$	None

Intermediate hilo Tracheal Tube cuff

In spite of a large difference in the values of compliance of non-intubated cuff between the HiLo and the Inter hilo, the values of compliance of intubated cuffs were identical. The surface area available for nitrous oxide diffusion of the Inter hilo cuff (4.03 cm^2) was smaller than the value of the HiLo cuff (5.82 cm^2) because the degree of folding was less in the Inter hilo. The smaller surface area of the Inter hilo accounted for the longer diffusion time (11 min) compared with the HiLo cuff (7.8 min). Because the volume of intubated cuff of the Inter hilo was less than the residual volume, all of the cuff pressure, 20 cm H_2O, would be transmitted to the tracheal wall, and the cuff membrane should fold—although the degree of folding was less than with the HiLo cuff. In spite of the similar values for diffusion rate, the diffusion time of the Inter hilo cuff was one-half as short as the Shiley cuff because of the low compliance of intubated cuff of the Inter hilo.

Shiley Low Pressure Endotracheal Tube cuff

The Shiley cuff showed the lowest compliance of non-intubated cuff; however, the compliance of intubated cuff was twice as great as the values of the HiLo and the Inter hilo cuffs. This high compliance of intubated cuff could be explained by a large expandable free area. Because the volume of intubated cuff was larger than the residual volume, the tracheal wall pressure was less than the indicated cuff pressure, 20 cm H_2O, and the cuff membrane should not fold. Therefore, the surface area available for nitrous oxide diffusion was limited to the free area not in contact with the tracheal wall. The diffusion time of the Shiley cuff (23.6 min) was almost three times longer than the HiLo (7.8 min), and twice as long as the Inter hilo (11.1 min). Less nitrous oxide diffused through the unit area of the Shiley cuff membrane during 1 min than with the HiLo.

DISCUSSION

The materials used in the study were readily available in the operating suite. The designs were simple and could be reproduced easily, yet yielded relatively accurate and useful clinical information. To maintain simplicity, we did not try to correct for minor variations such as change in volume caused by the compression of air, the residual volume was measured at cuff pressure (2 cm H_2O) instead of atmospheric pressure, and the volumes expressed as the volume of cuff included the volume of the pilot balloon. However, these minor variations should not alter the interpretation of our results.

We have reported that, when more than 50% nitrous oxide was administered in clinical anaesthesia, the times to double and treble an initial cuff pressure of 20 mm Hg, were 30 and 70 min, respectively for the HiLo tube, and 40 and 130 min, respectively for the Shiley tube. Compared with the Shiley cuff, the HiLo cuff has a large residual volume, a greater surface area, and a thinner cuff membrane (0.033 *v.* 0.135 mm) (Bernhard, Yost and Turndorf, 1978). These characteristics produce the highest compliance when measured outside the "trachea". However, when the cuff is inflated inside the rigid mock trachea, a large portion of the surface area of the cuff is in contact with the tracheal wall and loses its elastance. Only that small portion of the surface area which is free of contact with the tracheal wall retains its elastance and is expandable. The compliance of the intubated cuff depends mainly on this expandable free area. The inflated HiLo and Inter hilo cuffs in the trachea adopt a cylindrical shape, and the expandable free area spreads out horizontally. The inflated Shiley cuff resembles a spindle shape, and the expandable free area spreads out less than the horizontal angle. Therefore, the horizontally flared surface area of HiLo cuff has a smaller surface area than the slanted Shiley cuff, accounting for the lower compliance of the former.

The only difference between the Inter hilo and the HiLo cuff is the shorter length of the cuff on the Inter hilo. When these floppy cuffs were inflated in the "trachea", the expandable free area of cuff became identical, as did the compliance. Our study demonstrated that, in spite of a large difference between these two cuffs in the value of compliance of non-intubated cuff, the difference in compliance was abolished upon intubation.

Diffusion of nitrous oxide into an air-inflated cuff depends on the partial pressure gradient of the nitrous oxide across the cuff membrane, the surface area available for nitrous oxide diffusion, and the specific diffusion rate of nitrous oxide through the cuff membrane.

The diffusion time of the HiLo cuff was less than that of the Inter hilo, despite the fact that both cuffs were made of the same material, had equal expandable free areas and identical values of compliance of intubated cuff. When both floppy cuffs were inflated in the trachea, the cuff membrane folded. The folding could increase the area for diffusion of nitrous oxide, without affecting its compliance. Despite the identical expandable free areas, the surface area available for the diffusion of nitrous oxide in the HiLo cuff was greater than in the Inter hilo cuff because the HiLo cuff had a higher degree of folding. The different cuff volumes between these two cuffs does not seem to affect the diffusion time. During the specific diffusion rate study, we observed no difference in the amount of nitrous oxide diffusing through the unit area of the cuff membrane per hour with cuff volumes of 10 and 20 ml.

When both intubated and non-intubated cuffs are inflated with a given volume of air, the pressure of the intubated cuff will be greater than the non-intubated cuff if the intubated cuff exerts its pressure against the tracheal wall. The difference in pressure between the intubated and non-intubated cuff is the pressure transmitted to the tracheal wall. This relationship was described as $P_{\mathrm{tw}} = P_{\mathrm{int}} - P_{\mathrm{non\text{-}int}}$. This equation can also be applied in estimating the degree of folding. If $P_{\mathrm{tw}} < P_{\mathrm{int}}$, the cuff should not fold.

At the residual volume, the cuff is maximally expanded before being stretched. If the volume of intubated cuff is less than the residual volume, the cuff membrane should fold because the cuff cannot be fully expanded at the volume of intubated cuff. If the volume of intubated cuff exceeds the residual volume, the cuff should not fold because the cuff membrane is already stretched before reaching the volume of intubated cuff. The degree of folding should be related to the difference between the residual volume and the volume of intubated cuff. The surface area available for nitrous oxide diffusion is included in two areas, the expandable free area and the channelled area created by the folding.

Because the residual volumes of the HiLo and Inter hilo cuffs are larger than the volumes of intubated cuff, all of the cuff pressure is transmitted to the tracheal wall and both cuffs fold in the trachea, but the degree of folding was greater with the HiLo cuff. However, the residual volume of the Shiley cuff is less than the volume of intubated cuff; therefore, the estimated tracheal wall pressure is the difference between the intubated cuff pressure, 20 cm H_2O, and the non-intubated cuff pressure generated by 8.5 ml of air. In our experimental settings (tracheal tube, 7 mm i.d., inserted to a mock trachea, 20 mm i.d.), the cuff pressure of the Shiley tube (20 cm H_2O) may not provide an adequate tracheal seal for positive pressure ventilation. The large surface area of the Shiley cuff, which represents the expandable free area, accounts for its high compliance of intubated cuff. The diffusion time should be shortened by the large surface area, but it is counteracted by the low specific diffusion rate and the high compliance of intubated cuff. If the Shiley cuff pressure is adjusted to exert the same tracheal wall pressure, 20 cm H_2O, as the HiLo and Inter hilo, all measured and derived variables of the Shiley cuff should be different.

Even though the simulated mock trachea used in our laboratory investigation is quite different from the human trachea, the study seems to yield logical answers to the questions raised during our previous study in patients (Kim, 1980).

When low-pressure cuffed tracheal tubes are used for short-term intubation, conclusive clinical evidence of the superiority of one type of tracheal tube over another (Stanley, 1975; Homi et al., 1978) or of serious tracheal damage caused by overinflation of the cuff is lacking. However, it may be still good practice to maintain tracheal wall pressure low while maintaining a seal, because minor injury to the tracheal mucosa and deterioration of the compliance of tracheal muscle (Leverment, Pearson and Rae, 1975) can be caused by overinflation of the cuff (Dobrin and Canfield, 1977; Nordin, Lindholm and Wolgast, 1977). In addition, attention to tracheal wall pressure may prevent other complications such as the herniation of the cuff (Ward, Gamel and Benumof, 1978), or the collapse of the lumen of the tracheal tube (Perel et al., 1977). If the pressure injury occurs with the overinflated large-volume cuff, a wider area of tracheal mucosa or localized areas under the folds are vulnerable. Unavoidable folding with the large-volume cuff cannot only be a potential source of tracheal aspiration (Pavlin, VanNimwegan and Hornbein, 1975; Bernhard et al., 1979) but may also provide additional surface area for the diffusion of nitrous oxide. The main advantage claimed by those who advocate large-volume, low-pressure tracheal tubes is that a tracheal seal can be obtained with a low cuff pressure, since the cuff deforms to conform to the shape of the trachea (Crawley and Cross, 1975). This claim should be valid as long as the cuff pressure is low. However, without proper control of cuff pressure during anaesthesia, a dangerously high tracheal wall pressure can build up in a shorter time with this type of large-volume cuff than with the low-volume cuff.

In conclusion, we found no evidence from this laboratory investigation to support the superiority of the large-volume, low-pressure over the low-volume, low-pressure cuffed tracheal tube. The selection of tracheal tube cuffs cannot replace the preventive measures against overinflation of the cuff during anaesthesia. We believe that specification of the residual volume for each tracheal tube cuff would give meaningful information regarding the nature and expected performance of the cuff when in the trachea, and some indication of the relationship between cuff pressure and tracheal wall pressure.

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ASSESSMENT OF THE HEWLETT–PACKARD HP47210A CAPNOMETER

S. M. KINSELLA

SUMMARY

The Hewlett–Packard HP47210A Capnometer, a "mainstream" infra-red carbon dioxide analyser, has a sensor in-line with the patient circuit. The calibration apparatus is included within the unit, and an internal microprocessor corrects for the presence of nitrous oxide and varying concentrations of oxygen. Maximum error was 0.37 kPa for carbon dioxide partial pressures less than 5.3 kPa, and less than 3.6% for partial pressures of carbon dioxide greater than 5.3 kPa.

Instantaneous measurement of carbon dioxide concentration in respiratory gases is achieved by passing infra-red radiation through a sample and measuring the amount absorbed. Kalenda (1980) classified infra-red analysers into "sidestream" or "mainstream", depending on the siting of the radiation source and detector. In sidestream instruments the measuring chamber is placed inside the body of the instrument and gas is sampled at a constant rate from the patient's breathing system through fine-bore tubing. Mainstream instruments have a cuvette in series with the patient's airway across which the infra-red source and detector are aligned; thus all the respired gases are within the light path. These latter instruments may have problems with calibration drift and zeroing and, in common with all infra-red analysers, the presence of certain other gases may alter carbon dioxide absorption by collision broadening. The Hewlett-Packard HP47210A capnometer is a recently introduced mainstream analyser and is the subject of this communication.

DESCRIPTION

The instrument (fig. 1) consists of an adaptor in series with the airway, and a sensor which clips onto this adaptor and plugs into the processor box via a 2.4-m lead. The calibration apparatus is integral with the processor box.

The airway adaptor is cast in aluminium and has parallel windows a standard distance apart for all adaptors. It is fitted into the patient's airway using disposable plastic connectors and has a deadspace of 15 ml. It is heated by the sensor to prevent condensation of expired water vapour and can be sterilized by autoclaving or with ethylene oxide.

The sensor assembly (fig. 2) measures 5.3 × 3.2 × 3.6 cm and consists of: an infra-red source; a rotating filter wheel in which there are two sealed cells (one containing nitrogen and the other a known concentration of carbon dioxide) and an open cell; two parallel windows which line up with those in the airway adaptor; and an infra-red sensor. The filter wheel is driven by a d.c. motor at 2400 rev min^{-1} and gates the signal to reject signal drift. The temperature of the infra-red sensor has to be carefully controlled to ensure that it is responding to a constant infra-red wavelength. One section of the electronics, microprocessor controlled, deals with sensor head functions, providing power for the motor drive, infra-red source, and infra-red sensor heater, and the feedback control of the motor drive and the temperature of the infra-red sensor.

The processor box weighs 7.7 kg and measures 19.1 × 21.3 × 38.1 cm. It contains an analogue-to-digital converter for the incoming signal from the sensor and a microprocessor unit. When the instrument is being used clinically, the sample is assumed to be saturated with water vapour and to have a minimum inspired oxygen concentration of

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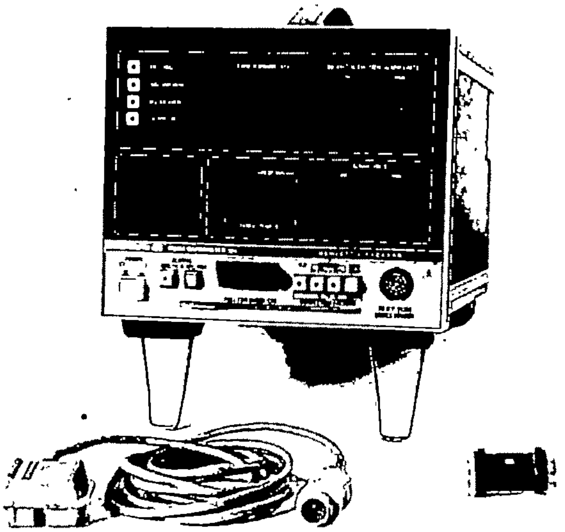

FIG. 1. The instrument.

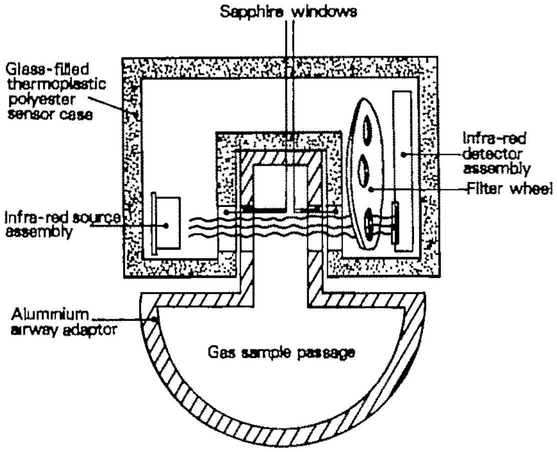
Sapphire windows
Glass-filled thermoplastic polyester sensor case
Infra-red detector assembly
Filter wheel
Infra-red source assembly
Aluminium airway adaptor
Gas sample passage

FIG. 2. Cross-sectional diagram of the sensor head.

21 %; the signal is corrected automatically for this by the microprocessor. There are switches for the presence of nitrous oxide, and for inspired oxygen concentrations of either 21–50 % or greater than 50 %, which apply further corrections. There are two front panel digital displays, one for instantaneous, end-tidal or inspiratory minimum carbon dioxide partial pressure, and one for respiratory rate. High and low alarm limits can be set for end-tidal carbon dioxide partial pressure and respiratory rate; the microprocessor can also detect and warn of a large number of error conditions. There are rear panel output sockets for instantaneous and end-tidal carbon dioxide partial pressure and respiratory rate. Values of 0 kPa and 6 kPa, and 0 and 75 b.p.m. can be selected for calibration of any attached recorder.

The calibration apparatus consists of two reference cells and two calibration buttons contained in a moulded plastic unit, 7.5 × 3.3 cm, mounted on the front panel, which is so shaped that the sensor unit can be clipped over one or other cell. This is called the "calstik". The "lo-cal" cell contains 100 % nitrogen for zero calibration; the "hi-cal" cell contains a known partial pressure of carbon dioxide in nitrogen for span calibration – this value is printed on the stick. The windows of the cells are the same distance apart as those of the airway adaptor. When the stick is pulled to the "out" position, all correction factors are switched off; when pushed in, the calibration buttons and cells are inside the machine and protected, and the selected correction factors are applied for clinical use.

For verifying the accuracy of the instrument, the sensor head is clipped onto each cell, and after 3 min the value displayed is noted. If it is not within 0 ± 0.13 kPa for the lo-cal cell, or printed value ± 0.13 kPa for the hi-cal cell, the machine must be recalibrated by pressing the appropriate calibration button (keeping the sensor in place over the cell); this takes a further 3 min. Recalibration is also necessary if a different sensor is being used with a processor box. Because the length of the light path is fixed for all airway adaptors and the windows are of equal thickness, different adaptors can be used without recalibrating.

The correction factors applied by the microprocessor depend on certain physical conditions: the airway temperature should be 33 °C, the sample should be fully saturated with water vapour and at standard barometric pressure, and the inspired oxygen concentration should be 21 %, 35 % (when the "21–50 %" oxygen switch is on), 75 % (when "$O_2 > 50\%$" is on) or 62.5 % (when "$O_2 < 50\%$" and nitrous oxide switches are on). If these conditions do not hold true, the reading of the carbon dioxide partial pressure may become less accurate, and in these circumstances the operator may calculate the error, using various equations (as given in the instruction manual). The order of magnitude of these errors as claimed by the manufacturers is as follows: if the airway pressure changes by ± 5 kPa there is a ± 5 % change in the reading, temperature ± 5 °C will

Table I. *Accuracy*

	Digital		Analogue	
	Carbon dioxide range		Carbon dioxide range	
	< 5.3 kPa	> 5.3 kPa	< 5.3 kPa	> 5.3 kPa
Maximum error	0.37 kPa	3.57%	0.32 kPa	2.00%
Manufacturer's allowable error	0.33 kPa	5.5%	0.27 kPa	5.0%

produce a ±1.6% alteration in the reading, and if the oxygen changes from the assumed value there can be up to 1.9% change in the reading.

There is an internal altitude switch to compensate for the ambient barometric pressure at different altitudes.

ASSESSMENT

Gas samples were mixed using Wösthoff 27/3F and 18/3F pumps (one pump for two-gas mixtures or two pumps in series for three-gas mixtures). These produced mixtures of known composition, with an accuracy of up to ±1.2%, as checked by Haldane analysis. Each sample was passed to the airway adaptor and thence vented via a section of corrugated tubing to ensure that pressure in the gas sample was atmospheric.

A thermocouple probe (Ellab TE3) was inserted to the airway adaptor to record temperature during sampling, and the instantaneous carbon dioxide output from the analyser was taken to a digital voltmeter (S.E. Laboratories S.M. 212).

The following gas mixtures were studied:

(i) 0–10% carbon dioxide; nitrogen as diluent
(ii) 0–10% carbon dioxide; oxygen as diluent
(iii) 0–2% carbon dioxide; 80% nitrogen; oxygen remainder
(iv) 0–5% carbon dioxide; 50% nitrogen; oxygen remainder
(v) 0–5% carbon dioxide; 50% nitrous oxide; oxygen remainder.

Each of these mixtures was made up on four occasions. All readings were corrected for barometric pressure and temperature.

For determination of systematic accuracy, readings were taken with mixtures (ii)–(v), with the calstik in and appropriate compensations applied. If a gas mixture contained an oxygen concentration between two particular ranges, for example 50% oxygen in the mixture being between "21–50%" and "$O_2 > 50\%$" ranges, then readings were taken with both compensations. These were compared with the gas mixtures supplied by the pumps (converteu to kPa). Accuracy was expressed as maximum error.

Because of the small number of readings of any given mixture, it was not possible to apply statistical methods for repeatability which was, therefore, expressed as a comparison of the maximum and minimum of the four readings for any given gas mixture, correction factors applied being similar.

RESULTS

Calibration

Zero-checking behaved as described in the manual, but the span check (hi-cal) sometimes required 4 min to equilibrate (rather than the stated 3 min). Recalibration was straightforward. When the instrument was left switched on for 8 days continuously, calibration drift was 0.02 kPa or less for both zero and span.

Accuracy and repeatability

Information on accuracy and repeatability is shown in tables I and II. Accuracy was checked for both the front panel digital display and the rear panel analogue output.

Linearity

Figures 3 and 4 show carbon dioxide percentage *v.* reading of the instrument for gas mixtures (i),

Table II. *Repeatability*

	Carbon dioxide range	
	< 5.3 kPa	> 5.3 kPa
Maximum difference	0.10 kPa	1.30%
Manufacturer's allowable limits of variation	±0.11 kPa	±2.0%

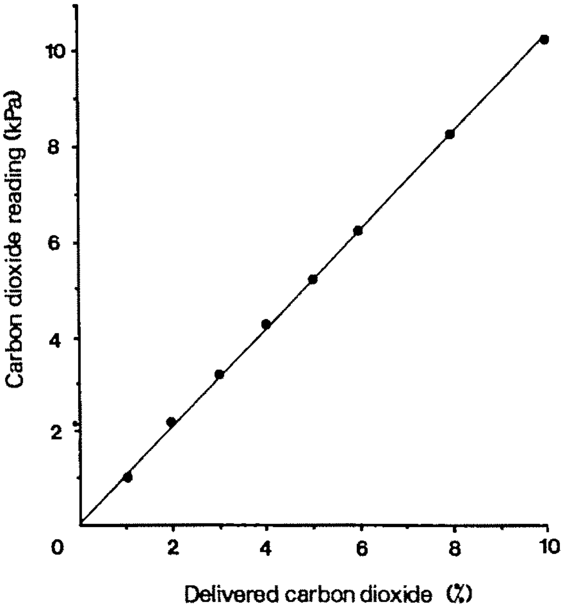

FIG. 3. Delivered carbon dioxide *v.* carbon dioxide reading for carbon dioxide in nitrogen mixtures.

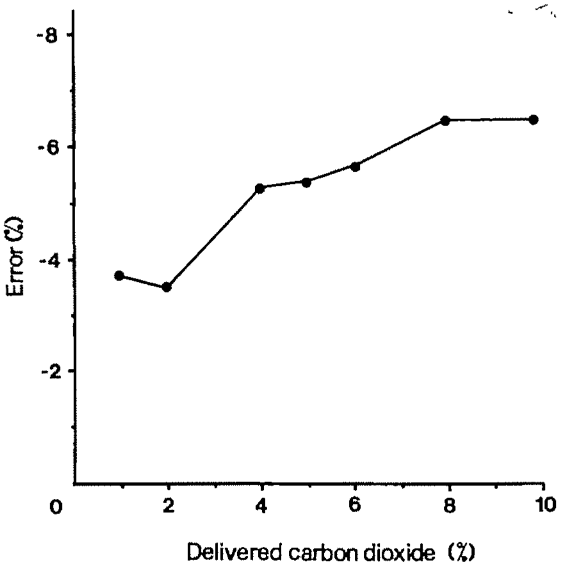

FIG. 5. Delivered carbon dioxide *v.* percentage change in reading when oxygen replaces nitrogen in a two-gas mixture.

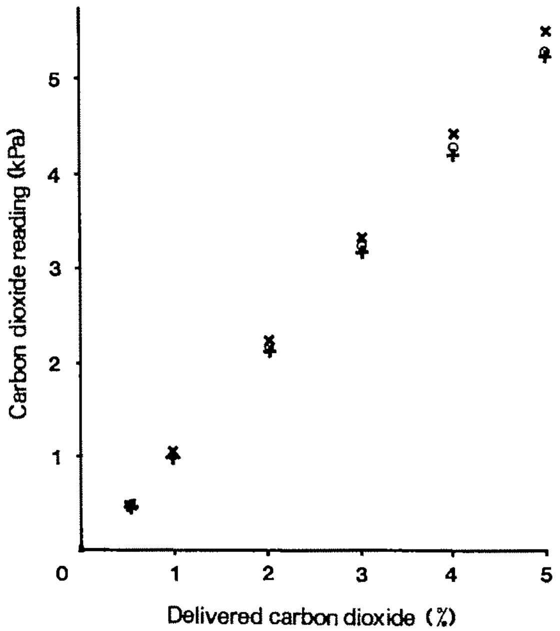

FIG. 4. Delivered carbon dioxide *v.* carbon dioxide reading for a three-gas mixture of carbon dioxide in oxygen up to 50%, remainder nitrogen or nitrous oxide. ○ = Nitrogen; × = nitrous oxide, no compensation applied; + = nitrous oxide, compensation on.

(iv) and (v), respectively. Figure 5 shows the change in reading when oxygen was substituted for nitrogen in a two-gas mixture, with no compensations applied. These graphs are drawn with pooled analogue data.

DISCUSSION

Ramwell (1957) showed the influence of various diluent gases on the absorption of infra-red light by carbon dioxide. Nitrogen increased absorption, when replacing oxygen, to a lesser degree than nitrous oxide. With no corrections applied, the instrument under test showed a 5.8% increase in carbon dioxide reading (from 5.03 kPa to 5.32 kPa) when 95% nitrogen was substituted for oxygen in a two-gas mixture, and a 4.3% increase (from 5.13 kPa to 5.35 kPa) when nitrous oxide 50% was substituted for nitrogen in a three-gas mixture with 45% oxygen remainder. These effects were additive.

Most modern infra-red carbon dioxide analysers, like the instrument under consideration, have nitrous oxide compensation mechanisms which decrease the sensitivity. This particular instrument can also compensate for variations in oxygen concentration. Because the analyser is calibrated with reference to a nitrogen diluent, the microprocessor corrects for the presence of oxygen by increasing the sensitivity.

The accuracy of this instrument was found to be within the stated limits for gas samples containing greater than 5.3 kPa of carbon dioxide; maximum error for gas samples of less than 5.3 kPa of carbon dioxide was 0.37 kPa rather than the stated limit of 0.33 kPa for the digital output, and 0.32 kPa rather than 0.27 kPa for the analogue output.

Blackburn and Williams (1980) reviewed two side-stream infra-red carbon dioxide analysers, the Datex CD101 and the Godart Capnograph Mark II. Using carbon dioxide–air mixtures, both instruments showed an accuracy exceeding that of the Hewlett–Packard; however, neither of these analysers provided a facility for oxygen compensation. The disadvantages of side-stream analysers are that the sampling tube can become blocked by secretions or water vapour and that, for an adequate breath-to-breath response time, a high sample flow rate may be needed, which may withdraw a significant volume of gas from the breathing system. The Hewlett–Packard does not suffer from these disadvantages and will be of special value in paediatric anaesthesia, or when using closed-circuit anaesthetic systems. A special airway adaptor for paediatric use with a deadspace of 2 ml will be available shortly.

Calibration checks of the Hewlett–Packard are simple and take a maximum of 7 min; recalibration needs no additional apparatus or gas supplies, and should only be necessary at weekly intervals or longer. Although it can be used within 5–10 min of switching on, maximum accuracy will normally be attained after 30 min. Accuracy will be affected by alterations in various physical conditions such as temperature, water vapour saturation, and pressure inside the aiway adaptor. This might be significant in certain unusual clinical situations such as in hyperbaric environments or when using profound hypothermia.

For testing of gas samples in the laboratory, especially non-physiological mixtures, it may be preferable to use the instrument in the calibration mode with the calstik out, and perform all relevant corrections by hand.

ACKNOWLEDGEMENTS

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MONITORING OF BRAINSTEM AUDITORY EVOKED POTENTIALS DURING BASILAR ARTERY OCCLUSION IN MAN

A. M. LAM, J. F. KEANE AND P. H. MANNINEN

SUMMARY

Brainstem auditory evoked potentials (BAEP) were recorded during surgery as a monitor o brainstem function in three patients undergoing posterior fossa surgery for clipping of basila aneurysms. In two patients, ligation of the basila artery, and of a vertebral artery, was associate with deterioration in BAEP and resulted i postoperative brainstem dysfunction. In the thir patient, postoperative transient neurological dys function occurred following temporary occlusio of the basilar artery and this correlated with intra and postoperative changes in BAEP. BAE monitoring is recommended where temporary o permanent occlusion of the vertebrobasil system is planned.

Since posterior fossa operations in the vicinity of the brainstem may be complicated by compression and ischaemia of the brainstem (Drake, 1981), the intraoperative monitoring of brainstem function is desirable. Although cardiovascular and respiratory signs have been used as indicators of the functional state of the brainstem during surgery, these reflect medullary activity alone and are modified by anaesthetic agents. Likewise, monitoring EEG activity is inadequate; it is influenced by anaesthetic agents and provides information on cortical rather than brainstem function.

Brainstem auditory evoked potentials (BAEP) are electrophysiological responses generated from stimulation of the auditory nerve. They provide information on the functional integrity of the auditory nerve pathway through the brainstem (Grundy et al., 1982; Raudzens, 1982; Grundy, 1983). With vascular decompression procedures such as the Jannetta Procedure for hemifacial spasm, Raudzens (1982) and Grundy and colleagues (1982) have demonstrated a good correlation between intraoperative changes in BAEP and postoperative VIIIth nerve function. During global brainstem ischaemia, which may occur during vascular occlusion of the vertebrobasilar system, or during extreme induced hypotension, monitoring of changes in BAEP may reasonably reflect, not just the integrity of the VIIIth nerve, but the well-being of the brainstem. We report on our experience with intraoperative monitoring o BAEP for this purpose in three patients wh underwent craniotomy for aneurysms of th posterior circulation.

PATIENTS AND METHODS

Methods of recording BAEP

BAEP was recorded from vertex (Cz) reference to the right or left ear lobes (A1 or A using silver–silver chloride disc electrodes a chored with collodion. To avoid cross contam nation, disposable plastic ear inserts connected transducers were used to deliver the audito stimuli. Whenever possible, BAEP was record before the induction of anaesthesia and th continuously during the surgical procedure. T evoked potentials were recorded with a Nicolet C 1000 averager and all tracings were replicat Electrode impedances were maintained at less th

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3 kΩ and at least 1000 sweeps were averaged. Monaural alternating clicks were delivered to the ear ipsilateral to the surgical site at an intensity of 60 dB above the patient's hearing threshold with contralateral masking of 30 dB above threshold at a rate of 21.1 Hz. Bandpass filters were set at 150–1500 Hz. In all three patients, anaesthesia was induced with thiopentone, fentanyl and nitrous oxide (in oxygen), and maintained with isoflurane and nitrous oxide in oxygen. Hypotension was achieved with an infusion of sodium nitroprusside in two patients and with increasing concentrations of isoflurane in the third patient (Lam and Gelb, 1983). Throughout the operative procedure, body temperature was maintained between 35 and 36°C using a thermal blanket and the end-tidal carbon dioxide tension between 30 and 34 mm Hg as monitored by an infra-red analyser.

Reproducible BAEP were obtained in all instances. Contralateral recordings were obtained whenever changes were seen on the side ipsilateral to the surgical wound. All patients had normal hearing thresholds before the operation. For reason of clarity, most tracings in the figures are not shown in duplicate.

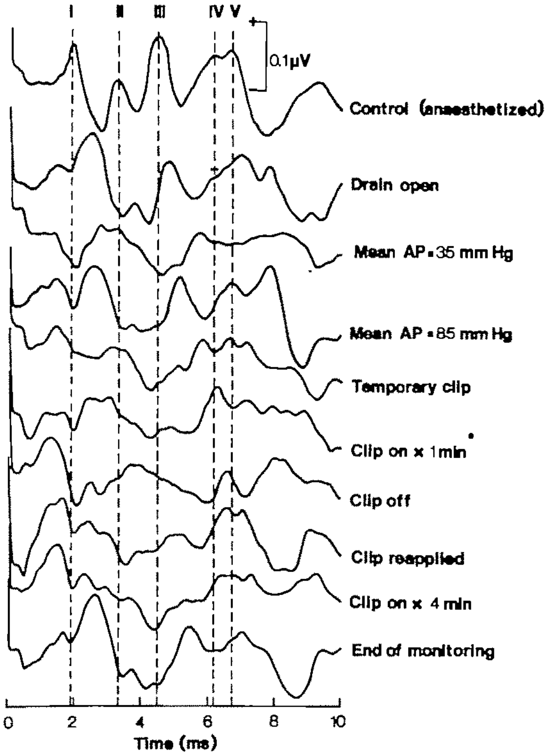

FIG. 1. Monitoring of BAEP in patient number 1; mid-basilar aneurysm. Deterioration was noted with the induction of arterial hypotension, and temporary occlusion of basilar artery. There was gradual improvement at the end, but the peak IV–V latency remained prolonged.

CASE REPORTS

Patient 1

A 33-year-old female of Jehovah's Witness faith presented with a history of coma producing subarachnoid haemorrhage as a result of a mid-basilar artery aneurysm. She had no neurological deficits before operation. Normal BAEP were obtained following the induction of anaesthesia. Spontaneous ventilation was allowed during the procedure and utilized as an additional monitor of brainstem function (Sellery, Aitken and Drake, 1973). To facilitate dissection of the aneurysm, mean arterial pressure (MAP) was decreased from 85 to 35 mm Hg with an infusion of sodium nitroprusside. The decrease in arterial pressure was immediately accompanied by a distortion of the BAEP waveforms with loss of IV–V complex, indicating possible brainstem ischaemia (fig. 1). MAP was then increased and the waveforms returned towards a normal configuration. A temporary clip was placed across the basilar artery and this caused a similar deterioration in the BAEP. The clip was removed and further dissection caused bleeding from the aneurysmal sac. The decision was then made permanently to occlude the basilar artery, since the patient was unwilling to accept blood transfusion. With application of the permanent clip, the BAEP again deteriorated with complete loss of IV–V complex and the patient's respiratory rate increased from 24 to 35 b.p.m. Gradual improvement in the waveforms occurred over the next 5 min, but at the end of the procedure the latency of the IV–V complex remained prolonged. Upon emergence from anaesthesia, the patient was alert and orientated, but had a mild right hemiparesis, bilateral VIth nerve palsy and a mild right VIIth paresis. The bilateral VIth nerve palsy was felt to be secondary to a pontine infarct.

Patient 2

A 45-year-old right-handed male suffered numerous transient cerebral ischaemic attacks as a result of a giant aneurysm at the vertebral–basilar junction. Although he had no preoperative neurological deficit, the BAEP waveforms showed an increase in latency of all peaks, indicating delayed brainstem conduction. (Peak V occurred at 7.72 ms; the upper limit of normal during isoflurane anaesthesia is 7.0 ms in our institution.)

As in the first patient, brainstem function during surgery was additionally monitored by the assessment of the pattern of spontaneous respiration. Following lumbar drainage of cerebrospinal fluid and the positioning of retractors the waveforms deteriorated, with a decrease in amplitude and an increase in latency of all peaks (fig. 2). Within 1 min of basilar artery occlusion with a clip, the patient became apnoeic, although no further deterioration in evoked potentials was seen. The clip was removed and then placed across the right vertebral artery. The BAEP remained abnormal at the end of the procedure (fig. 2). In the postoperative period the patient required airway and ventilatory support and was dysphagic with complete absence of laryngeal reflexes. Subsequently, he was discharged with a permanent tracheostomy, the gag reflexes remaining absent.

Patient 3

A 50-year-old female presented with an aneurysm at the bifurcation of the basilar artery. Before clipping of the aneurysm, she had mild confusion with no localizing signs. Satisfactory BAEP were recorded before and following the induction of anaesthesia. Application of the retractors caused an increase in latency of all peaks. MAP was decreased from 75 to 40 mm Hg by increasing the inspired isoflurane concentration to approximately 2.5% (Lam and Gelb, 1983). Immediately there was gross distortion and flattening of the BAEP waveforms (fig. 3A). MAP was then increased to 65 mm Hg and the BAEP reappeared within 1 min. Five minutes later, hypotension was again induced. Further dissection was difficult and again the BAEP became unrecordable for a period of 5–6 min. Utilizing temporary occlusion of the basilar artery, the neck of the aneurysm was clipped successfully. MAP was increased to 70 mm Hg, retractors were withdrawn from the surgical field and the BAEP waveforms started to return towards a normal configuration. However, at the end of the procedure, they remained abnormal with the latency of the IV–V complex very much prolonged from its awake control value (fig. 3B).

Recovery from anaesthesia was extremely slow; the patient was drowsy and demonstrated a mild quadriparesis and bilateral IIIrd nerve palsy. Her condition was remarkably improved at 36 h when she became lucid and orientated. At this time a repeat recording of BAEP was shown to be normal and similar to that obtained while the patient was awake before the operation.

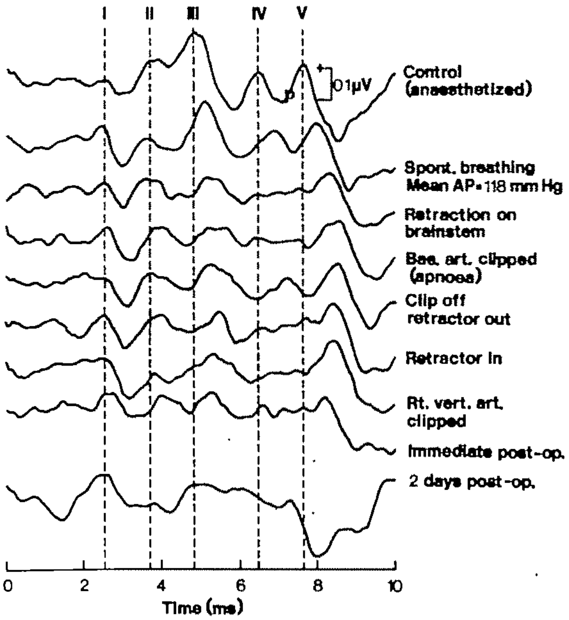

FIG. 2. BAEP changes in patient number 2; vertebro–basilar aneurysm. Loss of amplitude peaks III, IV and prolongation of peak V was observed with retraction of brainstem. BAEP remained abnormal at the end of the procedure.

DISCUSSION

Previous reports have demonstrated the potential use of intraoperative BAEP monitoring during posterior fossa surgery (Hashimoto et al., 1980; Little et al., 1983). These three patients further demonstrate the utility of intraoperative BAEP monitoring to predict and, possibly, to prevent brainstem dysfunction in complicated neurovascular procedures when temporary or permanent occlusion of the vertebrobasilar system may be necessary. In the first two patients, spontaneous breathing was also allowed and utilized as an additional means of monitoring brainstem function. In both patients, changes in respiratory pattern were preceded by changes in BAEP waveforms. Thus, it appears that BAEP may be a more sensitive monitor of brainstem function. More interestingly, in the second patient, although changes in BAEP preceded changes in respiratory activity, the onset of complete apnoea was not accompanied by

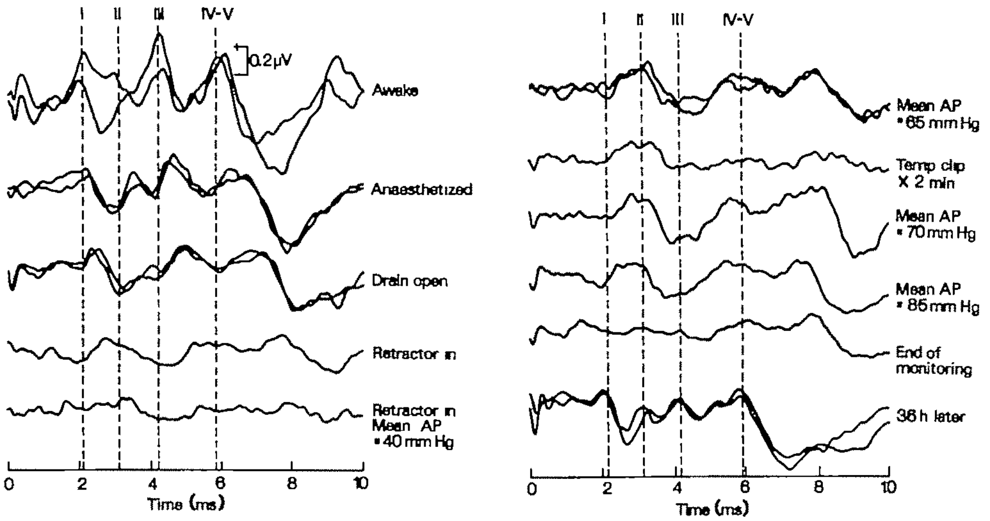

FIG. 3. A: BAEP changes in patient number 3; basilar bifurcation aneurysm. Note complete loss of BAEP with retraction and arterial hypotension. B: BAEP improved with increase in arterial pressure, but deteriorated again with temporary occlusion of the basilar artery. BAEP remained profoundly abnormal after operation, but returned to normal 36 h later when clinical condition improved.

further deterioration in BAEP. This is not entirely surprising, since the auditory nerve enters the brainstem at the pontomedullary junction and the pathway is more diffuse in nature compared with the respiratory centre which is situated lower in the medulla. Observations in these two patients suggest that, although BAEP monitoring may be more sensitive, the additional monitoring of respiratory activity may be valuable when deterioration in the former occurs.

In the first two patients, although changes in BAEP were clearly observed, there was no appropriate intervention therapy because of the nature of the lesion. The resultant postoperative neurological deficits confirmed the predictive value of the intraoperative changes in BAEP. Although the neurological deficits were not prevented, the changes at least warned the anaesthetist of potential problems in the immediate recovery period, and indicated that extra supportive care might be required.

In the third patient, changes in BAEP were evident simply with a decrease in systemic arterial pressure, suggesting that the lower threshold of autoregulation had been exceeded. This is not surprising, considering the presence of the retractors in the proximity of the brainstem, the pressure under which can be considerable but not monitored. Because of the changes in BAEP, attempts were made to increase the arterial pressure to a higher value and the retractors were immediately withdrawn upon application of the clip across the aneurysm. Despite these efforts, the BAEP remained abnormal at the end of the procedure and this again correlated with postoperative neurological dysfunction. Thirty-six hours later the clinical status improved, as did the BAEP. Thus there was an excellent correlation between the electrophysiological monitoring and the clinical condition. It further suggested that the changes observed during the procedure were ischaemic in nature and that, had the arterial pressure been allowed to remain at the lower value for a longer period of time, the patient may have suffered permanent rather than transient neurological dysfunction. One may argue that the changes observed during isoflurane-induced hypotension may be artefacts resulting from the effect of isoflurane. However, previous work in our laboratory in human volunteers has demonstrated that the effect of isoflurane on BAEP is self-limiting, and that the waveforms can be recorded clearly even at an end-tidal concentration of 2% (Manninen, Nicholas and Lam, 1984).

Thus, we have demonstrated the utility of intraoperative monitoring of BAEP as a monitor of brainstem function during high-risk neurovascular procedures in the posterior fossa. In order to interpret the changes occurring during surgery, the body temperature and the end-tidal carbon dioxide tension should be maintained within as narrow a range as possible. Other factors such as age and sex, which may influence the latency of the peaks, are not important factors for this purpose, as each subject acts as his own control (Stockard, Stockard and Sharbrough, 1978). When deterioration in BAEP is observed, depending on the nature of the surgical procedure, either interventional therapy in the form of increasing the arterial pressure or alternative surgical therapy can be planned. Such monitoring may help to improve patient safety during high-risk procedures in the posterior fossa.

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We wish to thank Mrs L. Nolan for secretarial assistance and Drs C. G. Drake and S. J. Peerless for their co-operation.

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CORRESPONDENCE

ALLERGIC REACTION AFTER ATRACURIUM

Sir,—I would like to report the occurrence of severe cutaneous manifestations of allergy after a minute dose for skin testing with atracurium in a patient who, 24 h earlier, had developed a similar reaction after 0.6 mg kg^{-1} of the neuromuscular blocker.

An 11-year-old boy was admitted with abdominal pain, fever and nausea for 36 h. He had no allergies and no other medical antecedents. A diagnosis of acute appendicitis was made and he was transferred to the operating room. Arterial pressure was 105/70 mm Hg, heart rate 110 beat min^{-1} and respiration 18 b.p.m. Before induction, he received fentantyl 0.05 mg i.v. A rapid sequence induction was conducted with preoxygenation, cricoid pressure, atracurium 0.6 mg kg^{-1} followed by thiopentone 4 mg kg^{-1}. Intubation of the trachea was performed without difficulty and, thereafter, anaesthesia was maintained with oxygen and isoflurane in concentrations sufficient to achieve clinical anaesthesia. Within 1 min after induction, severe, diffuse erythema and papullae appeared on the pathway of the vein in which the cannula was sited, and progressed toward the neck, thorax, upper abdomen and face; a slight increase on resistance to inspiration was also noted, but no wheezing was heard. The intensity of the rash progressed with greater redness. After progressive worsening was observed, phenylhydramine 25 mg was given i.v., with gradual disappearance of the rash and the pulmonary compliance returned to normal. Arterial pressure, following a decrease to 90/60, gradually returned to preanaesthetic values. The remainder of the procedure was uneventful, without requiring further neuromuscular blockade. Twenty-four hours later, skin tests were conducted on the opposite forearm using atracurium 0.003 mg, thiopentone 0.06 mg and fentanyl 0.06 μg, intradermally.

Erythema and papullae (+ + +) appeared on the site of the injection of atracurium 4 min later, gradually progressing toward the arm, shoulder, neck, thorax, face and upper abdomen at about the same rate of appearance, intensity and extension as the one observed the day before. Thirteen minutes later, the same dose of the antihistamine agent was given i.v., with the signs and symptoms subsiding promptly.

No respiratory distress was noted and wheezing was not present, although the patient reported considerable pruritis on the areas where the rash was evident. The cutaneous injections of thiopentone and fentanyl failed to elicite positive responses.

The generalized erythema, papullae, slight hypotension and possible bronchospasm, occurring immediately after the injection of atracurium, in a patient without known allergies, or other sign of immunological aberration, introduces the possibility of atracurium eliciting a different type of immune reaction. Although the interpretation of skin testing has been questioned (Assem, 1983), it has been useful to determine what local anaesthetics can safely be given to supposedly allergic patients (Aldrete and Johnson, 1970), but not necessarily to identify those drugs to which they are specifically allergic (Aldrete, 1984).

Skin reactivity noted in this patient as indicated by positive skin reaction and the distribution and characteristics of the erythema suggest it to be of the "cholinergic" type, with mediator release from mast cells in the presence of IgE (Soter et al., 1980).

The lack of localized reaction at the sites of the injection of thiopentone and fentanyl ruled them out as possible causes. The immediate occurrence of the reaction soon after administration would suggest that no metabolites were as yet produced.

The triggering of the reaction of similar intensity, 24 h later, with about 1/300 of the dose given previously, further substantiates the causative relation to atracurium. Of concern, is the possibility that a patient given atracurium may have an unrecognized reaction and would later receive a second dose, or require a second anaesthetic hours or days later; were atracurium given again, a severe anaphylactic reaction may ensue after a normal dose.

Although the amounts of histamine released after atracurium (Basta et al., 1983) were reported to be lower than those produced after tubocurarine, signs of allergic responses have been reported following the former by various authors (Foldes et al., 1983; Gergis et al., 1983; Rupp, Fahey and Miller, 1983; Twohig, Ward and Corall, 1983). Until greater experience is attained with it, atracurium should be avoided in patients with other drug allergies and an antihistamine drug may be given as premedicant to prevent cutaneous and systemic manifestations of allergy.

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EFFECT OF NALOXONE ON LOSS OF CONSCIOUSNESS INDUCED BY I.V. KETAMINE

Sir,—It has been shown that ketamine interacts with opiate receptors, and that its agonistic action at these receptors is partially responsible for its analgesic effect (Smith et al., 1980). However, studies concerning the antagonism of ketamine-induced narcosis by naloxone have shown conflicting results. According to Kraynack and Gintautas (1982), the intraperitoneal injection of naloxone in rats did not alter ketamine sleeping time, whereas they observed a dose-related antagonism of ketamine narcosis by intra-cerebroventricular injection of naloxone. The data reported by Stella, Crescenti and Torri (1984) showing that ketamine anaesthesia is strongly antagonized by i.v. naloxone in man are thus very interesting.

We have tried to reproduce the results of Stella, Crescenti and Torri in 100 healthy young adult women. All were to undergo voluntary abortion, were unpremedicated and received an injection of naloxone 6 µg kg^{-1} followed, 5 min later, by an i.v. injection of ketamine 0.404 mg kg^{-1}.

Our results differ completely from Stella's as 52% of our patients lost consciousness; these results prove that i.v. low doses of naloxone do not prevent ketamine-induced narcosis, since ketamine 0.404 mg kg^{-1} is its ED_{50}.

These data seem to confirm that the hypnotic activity of ketamine is not exclusively mediated through opiate receptors, and that much higher doses of naloxone i.v. would be required to antagonize ketamine-induced narcosis.

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Sir,—It is very difficult to say whether the results reported by Amiot and coworkers differ from ours (Stella, Crescenti and Torri, 1984), because of statistical differences between the two groups of patients.

First, we evaluated ED_{50} for ketamine in a random sample of patients of both sexes, whose ages ranged from 20 to 50 yr. Amiot's patients were pregnant, premenopausal women. Most likely, the ED_{50} for ketamine may vary remarkably in these patients, compared with the values obtained in our studies. The dose of 0.404 mg kg^{-1} cannot be regarded as ED_{50} for his patients. In other words, it cannot be expected to cause loss of consciousness in nearly 50% of patients.

In summary, we have two dissimilar groups of patients coupled with two non-equipotent doses. Therefore, the two consciousness loss percentages are not comparable.

It would have been interesting to perform a comparison between placebo-treated patients of the same kind, in order to validate the percentage obtained in the naloxone-treated group. Despite to this, pregnancy-induced pharmacokinetic and pharmacodynamic interference between naloxone and ketamine cannot be ruled out.

It is difficult to state that ketamine induced loss of consciousness, since this drug provokes a peculiar state of dissociation. For this reason, during placebo comparisons, it is crucial to follow a double-blind experimental design, in order to minimize loss of consciousness evaluation errors, resulting from the subjectiveness of the clinician.

In our experience, other factors like injection speed and dilution volume also influence the results.

L. Stella
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"ESOPHAGEAL GASTRIC TUBE AIRWAY" – A POTENTIAL HAZARD

Sir,—We were most interested to read the report of the use of the "Esophageal Gastric Tube Airway" (EGTA) in a case of failed intubation during obstetric anaesthesia (Tunstall and Geddes, 1984). We feel that this apparatus presents particular advantages in some cases of difficult intubation. Conversion of unsatisfactory extradural anaesthesia to general anaesthesia after the abdomen is opened is occasionally required. Where tracheal intubation proves impossible in this situation, rapid movement of the patient to the left lateral, head-down position as part of the "Failed Intubation Drill" (Tunstall, 1980) may not be possible.

We should, however, like to draw attention to a potential hazard associated with the use of the oesophageal tube. There is a one-way valve situated within the lumen of the tube at the upper end which will prevent passage of gastric contents out of the tube. In use this valve may prevent spontaneous decompression of gastric pressure through the tube and predispose to oesophageal regurgitation (since the oesophagus is a distensible structure and the inflated oesophageal balloon cannot guarantee occlusion). A second problem may arise should the oesophageal tube happen to be passed into the trachea. Should this situation occur and be recognized, then it might be wished to ventilate the patient using the "Esophageal tube". When the valve becomes wet it will obstruct expiratory flow.

The EGTA was designed for use by paramedical personnel when ventilation is suppled by blowing into the mask (Gordon, 1977). This brings the face of the resuscitator close to the outlet

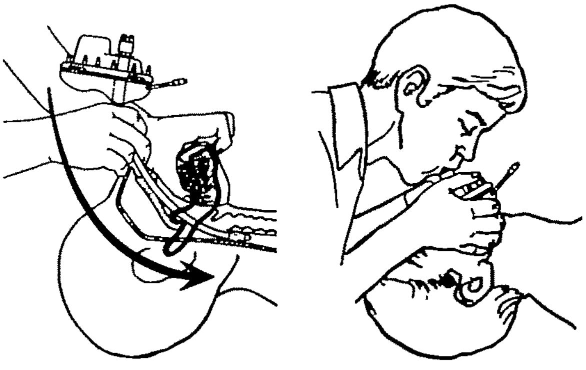

FIG. 1. Illustrations from the operating instructions supplied with the EGTA, showing the method of insertion of the oesophageal tube and its use in resuscitation.

of the oesophageal tube (fig. 1) and the valve is arranged to prevent reflux of gastric contents onto the operator. Gastric decompression is performed by passing the supplied small gastric tube through the oesophageal tube, bypassing the valve. Incidentally, we note that the illustration in the supplied operating instructions (fig. 1) shows the operator blowing down the oesophageal tube!

We recommend that anyone using the EGTA in an obstetric patient should, as a matter of course, pass the supplied small gastric tube through the oesophageal tube as soon as the EGTA is passed, and that it should stay *in situ* until the apparatus is removed.

In the unlikely event of tracheal placement of the oesophageal tube, the tube could be cut below the valve and a Portex connector used to avoid expiratory obstruction.

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Sir,—Drs Corke and Jackson have rightly enlarged on the problem of inadvertent tracheal intubation with the "Esophageal Gastric Tube Airway" (EGTA). They have also drawn attention to the fact that the suppliers send with the EGTA an illustration showing a rescuer blowing down an EOA (esophageal obturator airway). This could be confusing, as the EGTA and EOA are two quite different devices. In the case of the EOA one is meant to inflate down the oesophageal tube: the distal end is occluded and the supplied air or gas blows out of side perforations into the pharynx and then into the larynx.

While it has been pointed out that inadvertent tracheal intubation with the oesophageal tube is unlikely, the event with either the EGTA or EOA would in fact be very serious. One can imagine the problems caused by a supine (but tilted) 116-kg mother, whom one has failed to intubate, who is apnoeic and cyanosed and who has an obstructive tube in her trachea and a pool of vomit in her pharynx.

The solution to the problem is, first, to make sure that the device kept in the anaesthetic room of the maternity hospital is an EGTA and not an EOA. Second, the supplied oesophageal tube should be removed from the mask attachment and replaced with an uncut 8-mm Mallinckrodt endotracheal tube with a high volume–low pressure cuff. This endotracheal tube has a rolled edge Murphy tip which is potentially less traumatic than the usual pointed bevel. It is suitable for passage into the oesophagus. The modification is completed by adapting a second 15-mm connector to fit the outlet on the mask. If this was capped with a right-angled connector, any spurt of vomit up the oesophageal tube would be directed to the side.

The diagnosis of inadvertent endotracheal intubation would be assisted by being aware of the possibility. Should it occur, there would then be an endotracheal tube in the right place.

The above solution comes right back to Boys' (1983) recommendation, but with the added refinement of having a separate and additional aperture on the face mask to take the endo-oesophageal tube.

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CHOICE OF LOCAL ANAESTHETIC DRUG FOR EXTRADURAL CAESAREAN SECTION

Sir,—We wish to comment on the paper by Dutton and colleagues (1984) as they have misquoted us in their opening paragraph. At no time did we report that the introduction of more concentrated solutions of bupivacaine and etidocaine would provide a more rapid onset of sensory motor blockade "with better analgesia during labour". The sentence we believe they refer to states: "There are clearly considerable advantages to the use of stronger solutions of bupivacaine and etidocaine in performing surgical procedures as opposed to their use for producing analgesia for example in labour when motor block would be undesirable" (Scott et al., 1980).

We were interested to read the method as described in Dr Dutton and colleagues' unblinded study. They defined the end-point when administering the local anaesthetics as when "satisfactory sensory and motor blockade" had been established. To criticize then the properties of the agents under study is illogical, as it is really a failure of the technique when clearly "satisfactory" blockade had not occurred in many instances before surgery commenced. It is pertinent to note that the volumes of 1.5% etidocaine (8–26 ml) used were much less than either 0.5% bupivacaine (14–35 ml) or 0.75% bupivacaine (12–43 ml). Volume is a well recognized factor which influences the longitudinal spread of local anaesthetic solution in the extradural space. A valid comparison between different local anaesthetic solutions can only be made by strict control of the volumes used and by double-blinding.

We realize that the two- (or three-) stage top-up procedure to establish an extradural block is widely used and avoids some of the risks of systemic toxicity. However, this technique is unsuitable for the type of study in which agents are to be compared if it entails the use of a wide range of volumes. In the case of 0.5% bupivacaine, the repeated bathing of the spinal nerve roots may be necessary to achieve satisfactory blockade for surgery (which is unnecessary with the more concentrated solutions) and leads to the considerably slow onset time (mean 42 min) found in this study.

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Sir,—Thank you for allowing us the opportunity to reply to the letter from Drs McClure and Scott.

We apologize for the misquote in the first paragraph of our paper. This unfortunately occurred as a result of an oversight during our scrutiny of the edited manuscript immediately before publication. Our original manuscript read "...with a greater frequency of adequate analgesia (Scott et al., 1980)"–and made no reference to the use of higher concentrations of either drug during labour.

In response to their criticism of our study, we can only reiterate that we based our comparison of the efficacy of sensory analgesia upon observations of patients in whom we established extradural blockade which we considered adequate for the commencement of surgery, that is sensory blockade (loss of pinprick sensation) from S5 to T6 spinal segments bilaterally, with demonstrable motor blockade in the lower limbs. These appear to be the most common criteria recognized in this clinical situation and, as such, provide a logical end-point in determining the duration of onset of blockade. We believe that we have presented a valid clinical comparison of these local anaesthetic drugs despite the variation in volumes administered. We would point out that, in addition to the considerable variation in the volumes between the etidocaine and bupivacaine groups, there was also a wide variation in volumes administered to subjects within each group. One may conclude from this observation that, in the pregnant woman at, or near, term, the spread of a given volume of local anaesthetic solution within the extradural space is not easy to predict. We remain unconvinced that, in this particular situation and in the face of other variable factors (for example the patient's height, advancement in pregnancy, and the degree of distension of the extradural venous plexus), the injection of standard volumes of each local anaesthetic solution will produce a fairer or more valid comparison.

We accept that double-blinding may have been advantageous in this situation. It was, however, obvious to us before and during the formal study that the characteristics of the two agents, particularly regarding the onset of autonomic blockade, differed markedly. As we pointed out in the discussion section of the paper, we had to modify the procedure of fluid pre-loading in the women who received etidocaine and, for this reason, it was useful for the anaesthetist to be aware of which agent was being administered.

Drs McClure and Scott are correct in their assertion that the technique we have described is widely used in the practice of obstetric anaesthesia. For this reason, and also for the reason that the procedure of Caesarean section is one of the commonest surgical procedures carried out under extradural anaesthesia alone, we cannot agree that such a technique is inappropriate for the study of different local anaesthetic drugs.

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INTUBATING CONDITIONS WITH VECURONIUM

Sir,—The paper by Bencini and Newton (1984) appears to be planned essentially to test the old suggestion of differential paralysis of the respiratory and peripheral muscles by neuromuscular blocking agents. However, since most previous studies have not made direct comparisons, the authors may be attributing to previous workers views which they did not hold. Mirakhur and colleagues (1983) simply stated "that intubation could be carried out before the onset of complete neuromuscular block". However, in another paper on a similar topic, Clarke and Mirakhur (1983) stated that "intubating conditions when studied in a clinical sequence after thiopentone cannot be related closely to onset of neuromuscular block". This emphasizes what we believe to be the view of most anaesthetists, that thiopentone (with or without opiate) normally contributes greatly to the quality of intubating conditions. Therefore, we agree with Bencini and Newton in their statement that "One possible reason for these disparities [from the findings of ourselves and other workers] is the technique of anaesthesia associated with the intubation", since the anaesthesia used by Bencini and Newton (1984) was deliberately light.

Criticism is also levelled at other workers who use different criteria for assessing intubating conditions. Certainly, we agree that the patients who do not respond *at all* to intubation should be noted and that is what we have indicated (Mirakhur et al., 1983) by *excellent* conditions. The alternative term "ideal intubating conditions" (with a score of 1 or less) also used by Bencini and Newton corresponds to our "acceptable" conditions. It is not possible in any one patient to define a "Time to Optimal Intubation", since one can only assess conditions at the particular time at which intubation is attempted. One can only assess on a statistical basis the percentage of patients with a predetermined grading at a specified time. Certainly, intubating conditions recorded in patients having received a minimum amount of anaesthetic drugs would seem to be of little clinical value.

Surely expressing an intubation score (mean ± SD) has no statistical validity?

R. S. J. Clarke
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Mirakhur, R. S., Ferres, C. J., Clarke, R. S. J., Bali, I. M., and Dundee, J. W. (1983). Clinical evaluation of Org NC 45. *Br. J. Anaesth.*, **55**, 119.

Sir,—Drs Clarke and Mirakhur's letter addresses the two messages which we hoped our paper would convey to your readers.

First, as the correspondents rightly stated, this study was conceived and designed in order to test the hypothesis that vecuronium relaxes the respiratory (and, by inference, the laryngeal) muscle before the peripheral muscles. Intubation should consequently be possible when the peripheral muscles are still partially paralysed and the time to intubation would then be relatively short. This suggestion was put forward by Agoston and colleagues (1980) and later echoed by Krieg and co-workers (1980). Mirakhur and associates (1983) stated "that intubation could be carried out before the onset of complete neuromuscular block". This was, however, said in the context of the above-mentioned hypothesis and seemed to us to be providing supportive evidence for it. Clarke and Mirakhur (1983) later stated that the "intubating conditions when studied in a clinical sequence after thiopentone cannot be related closely to the onset of neuromuscular block". This statement points to the lack of correlation between peripheral neuromuscular block and intubating conditions. Which comes first is the important consideration. Indeed, in the same paper, Clarke and Mirakhur had noted earlier: "it was notable that in most patients tracheal intubating conditions were excellent well before the last twitch in the train-of-four was lost".

Second, we felt that the popular mode of assessing the intubating conditions provided by a neuromuscular blocker was inadequate in that it does not provide the practising anaesthetist with some of the most crucial information on the ability of a neuromuscular blocker to provide good clinical intubating conditions.

The information that most intubation studies provide is that, under an "average" type of anaesthesia – usually a deeper form of anaesthesia than minimal anaesthesia – a myoneural blocker will produce "excellent" intubating conditions, in a certain percentage of patients, with a given dose, at some minutes after its injection. This information is inadequate to the anaesthetist for several reasons. The "average" type of anaesthesia is of no value with a very ill patient in whom minimal anaesthesia must be applied. Relaxation for intubation will then have to be provided by the myoneural blocker, not by deep anaesthesia. The excellence of the intubating conditions is based on a complex score that is subjective and seems to mean different things to different people. The anaesthetist is thus not sure of the excellence of the intubating conditions that he should expect. Knowing only that a percentage of the patients will not react to tracheal intubation is of no use when faced with a perforating eye injury. The patient must not react to intubation.

These problems can be overcome by studies under light anaesthesia, simplifying the intubation score (taking as an end-point no reaction at all to intubation), and by noticing the doses as well as time after injection which produce no reaction in all patients. It is evident from most studies, once a certain dose is exceeded, that excellent conditions will be attained if the time to intubation is long enough.

This is what we called the Time to Optimal Intubation (TOI). It is certainly not possible to predict such a time interval in any one patient; this value can be achieved in large enough groups of patients by increasing the dose and the time to intubation in steps of, say, 30 s. The correspondents would have achieved this if, in their investigations, they had kept on increasing the dose of vecuronium and intubated the patients at ever longer intervals after injection of each dose of vecuronium. This method of assessment, besides being more simple and applicable to the most exigent clinical situation, will also do away with the cumbersome expression of an intubation score in terms of mean ± SD.

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SHORT ACTING NEUROMUSCULAR BLOCKERS AND ECT

Sir,—Few anaesthetists now have experience with the administration of electroconvulsive therapy (ECT) modified by the use of a competitive neuromuscular drug instead of suxamethonium. Recently, a patient was encountered who appeared to develop bronchospasm after the administration of suxamethonium for ECT. Although skin sensitivity tests were negative, it was decided to omit suxamethonium and use a competitive neuromuscular blocking agent. Initially, alcuronium 2.5 mg was used, but this did not provide satisfactory modification of the ECT.

Vecuronium was then used in view of its short duration of action and the possibility that it is less likely to release histamine. This proved satisfactory using the following technique: After the dose of the induction agent, vecuronium 2.0 mg was given i.v. The patient was ventilated with oxygen–halothane for 2 min and then ECT administered. The tonic and clonic response were very similar to that produced after administration of suxamethonium 30 mg. The effect of the neuromuscular blocking drug was then immediately and completely antagonized with neostigmine 2.5 mg and atropine 0.6 mg.

Others in a similar situation may find this technique useful.

M. E. DODSON
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USE OF VECURONIUM IN CARCINOID SYNDROME

Sir,—Anaesthesia for two patients with carcinoid syndrome is described, including the management of a patient in whom emergency surgery was required.

A 55-year-old woman presented for laparotomy with a gastrointestinal carcinoid tumour and multiple liver metastases. Oral premedication consisted of diazepam 5 mg and promethazine 25 mg, and anaesthesia was induced with fentanyl 100 µg, etomidate 15 mg (and pancuronium 6 mg). Intubation produced no adverse cardiovascular effects, but slight expiratory wheezing developed which persisted throughout the operation. Anaesthesia was maintained with 66% nitrous oxide in oxygen with increments of fentanyl 50 µg and vecuronium 2 mg. Hemicolectomy, hepatic dearterialization and portal vein cannulated were performed. Glycopyrrolate 0.6 mg and neostigmine 2.5 mg produced prompt and complete recovery from neuromuscular blockade, verified by the use of a nerve stimulator. The patient made an uneventful recovery, and was discharged from hospital 2 weeks later.

A 63-year-old lady presented with acute bowel obstruction caused by an ovarian carcinoid tumour. Hepatic dearterialization and portal vein cannulation had been performed on a previous occasion. She was rehydrated and premedicated with diazepam 5 mg and promethazine 20 mg by mouth. After preoxygenation, anaesthesia was induced with etomidate 15 mg, suxamethonium 75 mg was administered and the trachea intubated. Cricoid pressure was performed. After a few minutes the patient became flushed, but there was no bronchospasm and the arterial pressure and heart rate remained at their preoperative values. Ventilation was continued by hand using a mixture of 66% nitrous oxide in oxygen, and the flushing decreased over the next few minutes. Anaesthesia was maintained with fentanyl 100 µg, vecuronium 6 mg and the same gas mixture. Heart rate and arterial pressure remained stable, except during manipulation of the tumour when the arterial pressure increased briefly. One increment of fentanyl 50 µg and vecuronium 2 mg was needed. Surgery lasted 1 h and revealed widespread inoperable tumour. Reversal of neuromuscular blockade, using glycopyrrolate 0.6 mg and neostigmine 2.5 mg, was confirmed using a nerve stimulator. The patient recovered well from anaesthesia and surgery, but her condition gradually deteriorated, and she died 10 days later.

In 1976, Mason and Steane reviewed the problems of anaesthesia for patients with secreting carcinoid tumours and stressed the importance of reporting anaesthetic management, the choice of neuromuscular blocking drugs requiring careful consideration in such patients.

The use of suxamethonium is hazardous, as the fasciculations increase intra-abdominal pressure and release tumour hormones (Déry, 1971; Mason and Steane, 1976). Protection of the airway was the primary concern during induction of anaesthesia in the patient with bowel obstruction. The severe flushing which occurred after intubation was attributed to release of tumour mediators. Pretreatment with a small dose of a competitive neuromuscular blocker to reduce fasciculations may have been useful.

The patient for elective surgery was starved, therefore a non-depolarizing neuromuscular blocker could be given at induction. The ganglion-blocking and histamine-releasing properties of tubocurarine are undesirable (Sniper, 1952). It has been suggested that pancuronium is the drug of choice (Mason and Steane, 1976), and it was therefore used for the first patient, but it can cause tachycardia, hypertension and histamine release (Kelman and Kennedy, 1971; Bodman, 1978). In view of this, the newer neuromuscular blocking agents were considered. Atracurium has a novel mode of elimination and less cumulation, but it can also cause histamine release (Basta et al., 1982), and may be unsuitable for patients with carcinoid syndrome. Vecuronium lacks histamine releasing properties (Basta et al., 1983), is relatively free from cardiovascular effects and is antagonized readily (Fahey et al., 1981). As the first patient's condition was stable when a supplementary dose of relaxant was needed, vecuronium 2 mg was given. Good relaxation was produced, with no adverse effects, and reversal at the end of the procedure was prompt and complete. It was therefore chosen for the second patient, again with no adverse effects and prompt reversal. Perhaps the properties of vecuronium make it the drug of choice in these cases.

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HYPOGLYCAEMIA IN CHILDREN UNDERGOING OUTPATIENT PROCEDURES

Sir,—Dr Padfield (1984) in his study of blood glucose concentrations in children undergoing dental procedures concludes "that the young dental outpatient over the age of four years is not at risk from hypoglycaemia during anaesthesia."

Such may be the case, but the group shown by Thomas (1974) to be at risk in a study of inpatients, were those younger than the age of 47 months and weighing less than 15.5 kg. Only four such patients were included in Padfield's study (1984). I have had personal experience that would indicate that outpatients are at risk from hypoglycaemia.

A 30-month-old Caucasian female with a tooth root abscess underwent removal of a right upper quadrant D as an outpatient. She had nil by mouth for 12 h and had no previous medical or anaesthetic history. Anaesthesia was induced with nitrous oxide and halothane in oxygen and was maintained with the same mixture via a nasal mask. Total anaesthetic time was 7 min.

The recovery phase was prolonged. After 12 min the patient was noted to be well oxygenated with good tidal excursions but was unrousable, sweaty and had a tachycardia in excess of 140 beat min^{-1}. A Dextrostix (Ames) at this time recorded a blood sugar of less than 1.4 mmol litre^{-1}. Later laboratory analysis revealed the blood sugar to be 1.1 mmol litre^{-1}. After the administration of 50% glucose 15 ml she awoke within 90 s, with no neurological sequelae.

Senior (1973) has discussed whether children who became hypoglycaemic during starvation have a separate biochemical abnormality or are purely the extreme of a normal distribution. The combined number of patients younger than 4 yr in the studies of Graham (1979) and Padfield (1984) is 28. This is not enough to exclude a low but significant incidence of hypoglycaemia, as the example quoted above suggests.

The lesson is clear. Even in outpatients, when children are being anaesthetized, adequate carbohydrate intake may have to be ensured. Hypoglycaemia should be considered as one possible cause of unexplained alterations in conscious level in this age group.

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Sir,—Thank you for the opportunity to respond to Dr Harpin's letter, I am pleased that he has emphasized the fact that hypoglycaemia can occur in outpatients younger than 4 yr. However, children of this age group are naturally uncommon as dental outpatients, hence the small number in my study.

On checking my original data, I find that the four patients younger than 4 years had all eaten within the previous 5–8 h and thus had not starved for as long as Dr Harpin's patient.

It might be wise to defer patients younger than 4 yr to afternoon sessions, allowing them to have breakfast and thus curtailing the long overnight period of fasting.

A. PADFIELD
Sheffield

METASTATIC CARCINOMA IN THE EXTRADURAL SPACE

Sir,—The long-term cannulation of the extradural space in the management of pain is new, and the literature on possible complications sparse. We would like to draw the attention of your readers to a hitherto undescribed complication.

A previously healthy young man was found, at operation, to have an inoperable adenocarcinoma of the rectum with retroperitoneal spread. Scintigraphy demonstrated metastases in the skull, ribs, sternum, vertebral column and liver.

After operation his condition deteriorated rapidly, and he was managed with blood transfusion, systemic steroids and extradural morphine for the relief of pain.

An extradural catheter was inserted at the second lumbar intervertebral space. The insertion was easy and without complications. Morphine 8 mg was injected two to four times per 24 h, resulting in relief of pain without side-effects.

After 35 days of treatment increasing resistance to injection was experienced, and after 42 days (and a total of 115 injections) further injection was impossible. On examination the catheter seemed to be *in situ*, without any sign of kinking or other apparent reason to explain the loss of function. The catheter was removed and found to be intact.

Because of the poor condition of the patient a new catheter was not inserted, and he was managed with analgesics by mouth and subcutaneously until death occurred 6 days later.

At autopsy the skeleton was found to be infiltrated widely by metastases, in the spine located to the cancellous bone of the vertebral bodies. Histological examination of tissue from the site of the extradural catheter showed the extradural side of the dura mater covered with cell-masses of metastatic carcinoma, and the extradural space and the soft tissue between the two opposing spinous processes was infiltrated by cancer tissue. No cancer tissue was demonstrated in the central nervous system.

Loss of function of an extradural catheter in long-term therapy is usually caused by kinking, or external pressure to, the catheter. Also, gradual closing of the side-holes has been reported, possibly caused by local changes in temperature. Other well known complications that might cause occlusion of the catheter are extradural haematomas and abscesses, but occlusion by metastatic cancer tissue has, to our knowledge, never been described.

What caused the presence of metastatic cancer tissue in the extradural space is uncertain. Our investigations seem to indicate that these metastases were not present at the time of cannulation. Nothing has suggested that cancer cells were implanted by the cannulation procedure from osseous metastases, but perhaps by implantation of cells from nearby soft tissue metastases. Another explanation might possibly be lodgement of tumour emboli around the catheter, the soft tissue being already affected by non-specific inflammatory or foreign-body reactions.

Whatever the pathogenetic mechanism, one should remember that metastatic cancer invasion of the extradural space is possible and can cause obstruction of the catheter.

J. PEDERSEN
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CSF PHARMACOKINETICS OF EXTRADURAL MORPHINE

Sir,—We read the letter from Strube, Downing and Brock-Utne (1984) with great interest. We have been able to show that the cisternal cerebellomedullary CSF concentrations of morphine are dependent on the volume of the extradural injection (Chrubasik et al., 1984), suggesting that the risk of respiratory depression might be reduced with low-volume injections to the extradural space. We have further investigated the problem by using radioactively-labelled morphine in large and small dogs.

Three dogs, anaesthetized with pentobarbitone, were kept lying on their left side throughout the course of the experiment. Dog 1 (12 kg) and dog 2 (33 kg) received morphine 2 mg in 10 ml saline, into the extradural space at T7 and L3, respectively. The solution administered to dog 1 contained ^{3}H-morphine 0.25 mCi; that of dog 2 contained ^{3}H-morphine 1 mCi.

Dog 3 (32 kg) received morphine 2 mg in saline 1 ml (+^{3}H-morphine 1 mCi) before an extradural infusion of 8 mg (+^{3}H-morphine 5 mCi) over 48 h at T7. Cisternal cerebellomedullary CSF samples were taken at varying intervals and the counts per minute (ct min^{-1}) determined with a Packard Tricarb liquid scintillation spectrometer (Model 574).

Six large dogs, with a mean weight of 33 kg, and three small dogs, with a mean weight of 15 kg, received an extradural bolus injection of Iohexol 10 ml (iodine 300 mg ml^{-1}, Schering) to evaluate rostral spread by radiography.

Peaks were reached of 24000 ct min^{-1} (dog 1 at 30 min), 2800 ct min^{-1} (dog 2 at 40 min) and 1000 ct min^{-1} (dog 3 at 50 min), which subsequently declined to 70, 120 and 480 ct min^{-1}, respectively, after 48 h. The mean rostral spread of Iohexol was 12 ± 0.7 spinal segments in the larger dogs and 17 ± 1 spinal segments in the smaller dogs.

The cause of respiratory depression following the extradural administration of analgesics is most likely rostral intrathecal spread of morphine from the lumbar region to the ventricular system (Glass, 1984). Because intrathecal morphine concentrations increase dose-dependently following extradural administration of morphine (Jorgensen, Andersen and Engquist, 1982), the extradural dosage should be kept as low as possible.

Our results show that rostral extradural spread of morphine is dependent not only on the injection volume, but also on the size of the extradural space. It would be interesting to consider instances of respiratory depression in relation to the size and age of the patient.

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VENTRICULAR ARRHYTHMIAS AND ADRENALINE INFILTRATION DURING GYNAECOLOGICAL SURGERY

Sir,—Published reports in the last two decades have shown that cutaneous and mucosal infiltration of dilute adrenaline-containing solutions for surgical haemostasis during general anaesthesia may result in the development of ventricular arrhythmias (Katz, Matteo and Papper, 1962; Katz and Epstein, 1968). In a recent study (Low et al., 1984) the plasma concentrations resulting from the cervical infiltation of a mean dose of adrenaline 1.36 µg kg^{-1} in 0.5% bupivacaine were measured using high pressure liquid chromatography with electrochemical detection. The six patients studied were undergoing cone biopsies of the cervix and the anaesthetic technique involved spontaneous ventilation with nitrous oxide in oxygen and halothane supplementation. The surprising feature of this fine study was the observation that, despite a more than 18-fold increase in plasma adrenaline concentrations (from 1.01 ± 0.23 (SEM) nmol litre^{-1} to 18.6 ± 3.7 nmol litre^{-1}), no cardiac rate or rhythm changes were noted and no changes in arterial pressure were observed. The authors did not specify the site of cervical adrenaline infiltration and the speed of injection.

The cardiovascular sequelae from cervical adrenaline infiltration in this study are in marked contrast with our observations (Cunningham et al., 1984) when we studied the cardiovascular and metabolic effects associated with the cervical infiltration of adrenaline 1.5 µg kg^{-1} 1:200000 in 0.5% lignocaine in 10 patients having cone biopsies of the cervix under extradural anaesthesia, and a control group of eight patients receiving cervical infiltration with 0.5% lignocaine plain under a similar extradural anaesthetic technique. Following careful aspiration, the infiltration was performed over 2 min to the cervix at positions 3 and 9 o'clock. In the adrenaline-treated group, marked increases in heart rate and systolic, diastolic and mean arterial pressures over base-line were noted in the 2-min period following infiltration. Fifty per cent of the adrenaline-treated group developed ventricular irritability (three or more PVC) and significant glycogenolysis, gluconeogenesis, lactic acidosis and hypokalaemia were noted. Plasma catecholamine concentrations were not measured.

Many factors influence the incidence of adrenaline-associated ventricular arrhythmias: the patient's age, the dose (µg kg^{-1}) injected, the speed of injection, the vascularity of the site injected, the electrolyte balance, the adequacy of ventilation, the addition of lignocaine to the adrenaline solution and the volatile anaesthetic agent used (Karl et al., 1983; Johnston, Eger and Wilson, 1976; Atlee and Malkinson, 1980). Based on Low and colleagues', and our observations, it would appear that Katz's original guidelines for adrenaline injection during general anaesthesia (Katz, Matteo and Papper, 1962)—adequate ventilation, adrenaline concentration 1:100000–1:200000 and a dose not to exceed 10 ml in 10 min or 30 ml h^{-1}—should be modified for cervical adrenaline infiltration. The total dose injected should not exceed 1 µg kg^{-1}. The solution could be diluted to a 1:400000 concentration. The infiltration should be made to the less vascular anterior and posterior cervix sites; the infiltration, after careful aspiration, should be performed slowly over at least a 5-min period. These precautions, we have found, minimize the cardiovascular and metabolic changes associated with the systemic absorption of infiltrated adrenaline-containing solution, while at the same time providing satisfactory haemostasis.

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Br. J. Anaesth. (1985), 57, 938–941

BOOK REVIEWS

Plexus Anesthesia, Volume 1: Perivascular Techniques of Brachial Plexus Block. By A. P. Winnie. Published (1984) by Churchill Livingstone. Pp. 272; indexed; illustrated. Price £40.00.

The reviewer's first impression of this volume was that it would form a valuable addition to the literature on regional anaesthesia. No expense has been spared to make it a visually attractive and authoritative text on brachial plexus blockade by the lavish use of colour plates and anatomical drawings reproduced on fine grade paper. Unfortunately, the same meticulous concern with detail and presentation has not been given to the text, which is liberally bespattered with errors of spelling and syntax. One can only sympathize with Vestor Andersen who, "in a prospective study of 100 patients developed Horner's SYNDOME". Treated with "PNENYLEPHRINE", perhaps his "INEQUALLITY" of pupil size was "ASSYMPTOMATIC" – all errors contained in one column of text – page 241.

A major criticism is the failure of the bibliography to relate accurately to the text. Hundreds of references are provided at the end of each chapter, of which perhaps 50% are referred to in the text, yet names appear which are not included in the bibliography. As an example, Chapter IV has 108 listed references; 45 names appear in the text; six of these are unlisted. To add to the confusion, Moore is mentioned on a single occasion, yet 10 references are given against his name.

The book is at its best in the chapters on the anatomy and relations of the plexus, and on the techniques of anaesthetizing the plexus.

The quality of the illustrations is outstanding, the dissections meticulous, and most valuable is the presentation of the anatomy from the viewpoint of the clinician rather than the anatomist.

The descriptions of technique are clearly illustrated, the clarity of the few black and white drawings suggests that colour could have been used more selectively with considerable reduction in cost. The layout of this section leaves large areas devoid of text or illustrations—for readers' annotations?

The help of such a brilliant illustrator has perhaps tempted the author to include illustrations which are superfluous to understanding of the text, for example pages 53, 160. Also, to utilize the advice given on page 205 "when charting the extent of anaesthesia following an interscalene block, it is more appropriate to do so utilising a dermatome chart, rather than a peripheral nerve chart", it is surely necessary that the next includes a dermatome chart.

The exceedingly long historical section will unfortunately tempt readers to scan its contents rapidly; they may therefore miss the only detailed reference to tourniquet pain (p. 82). An interesting feature of this section is the inclusion of the original descriptions of the various techniques, allowing the text to act as a commentary upon them and argue the case for the author's concept.

Chapters IV and V lack cohesion and balance. They offer neither a comprehensive survey of their subject matter and its literature nor a guide to the avoidance and treatment of side effects and untoward sequelae. Omissions include basic pharmacology, which would seem appropriate in a volume containing a large section on pharmacokinetics, choice of local anaesthetic agents and toxicity. Surprising also is the lack of attention paid to the treatment of intravascular injection and overdose, whilst cardiac arrest is dismissed with a report from the literature (p. 246).

No advice is given on the essential requirement of having secure venous access before initiating the block, or having available at all times the equipment to deal with all major untoward sequelae.

Regrettably, the irritations caused by the poor quality of the editing and proof reading, allied to the lack of balance in the later sections, have spoilt the reviewer's enjoyment of the many important and illuminating sections of the book. A more stringent editorial policy on presentation, illustrations and text would result in an equally visually pleasing and educative book, which would be less expensive and much more enjoyable read.

R. S. Neill

Advances in Morphine Therapy: The 1983 International Symposium on Pain Control. Edited by E. Wilkes and J. Levy. Published (1984) by the Royal Society of Medicine. Pp. 167; indexed; illustrated. Price £12.50.

This volume is published by the Royal Society of Medicine in its International Congress and Symposium series. The first section contains papers pertaining to acute pain relief, and the remainder of the book is devoted to the treatment of chronic pain. The large majority of papers discuss the use of a sustained release oral preparation of morphine, reflecting the sponsorship of the Symposium. Discussion has been omitted, although chairmen's summaries are included. The book may be of value to those seeking information on oral sustained release morphine.

A. R. Aitkenhead

Clinical and Resuscitative Data (3rd Edn). By R. P. H. Dunnill and M. P. Colvin. Published by Blackwell Scientific Publications, Oxford. Pp. 213; illustrated; indexed. Price £8.50.

I feel sure readers will recognize the title of this little data compendium and indeed many may have a well-worn copy of one of the previous editions to hand.

The topics covered in this, the 3rd edition, are divided into 13 sections, three more than previously, and the sections are arranged in alphabetical order. The new sections are entitled Burns, Diabetic Control and Toxicology. Most of the data presented in these sections were previously incorporated in subsections, although the information concerning the management of hyperglycaemia has been extensively revised and guidelines on the control of diabetes in the surgical patient have been added.

The remaining sections have all been revamped: tables are easier to read, references have been updated and additional information has been included. A four-page index is another new feature which will make the book easier to use.

As the book is written by two anaesthetists, I feel it is unsatisfactory that the adult dose of many anaesthetic agents is given as a standard amount, rather than an mg kg^{-1} basis. I am also surprised that, in their guidelines for the treatment of injury-induced hypovolaemia, the authors choose to name one particular colloid solution to the exclusion of any other agent.

Despite these two points, the authors have indeed succeeded not only in updating, but also in improving, this book. It costs £8.50 and at that price continues to deserve a place in the white coat pockets of both junior and senior medical staff.

Susan M. MacVicar

Inhalation Anaesthesiology. Clinics in Anaesthesiology. Edited by R. I. Mazze. Published by Saunders. Pp. 524; indexed; illustrated. Price £11.75.

This volume was published in 1983 and references are generally well up to that date although, of course, there have been important subsequent developments in the field. It is not intended as a comprehensive text book, but is a series of 17 reviews, written to a high standard and on well chosen topics.

The chapters fall into two distinct groups. Twelve are specifically devoted to inhalation anaesthesia, while the remaining chapters are devoted to subjects of wider application, relevant to anaesthesia as a whole. They comprise reviews of calcium entry blockers, anaesthesia for the morbidly obese, anaesthetic management of bronchospastic disease, outpatient anaesthesia and anaesthetic accidents. All are authoritatively written by experts in their respective fields and their inclusion is welcomed.

The other 12 chapters are highly selective state-of-the-art reviews of aspects of inhalation anaesthesia which are of special contemporary interest. Dr Forrest contributes a concise account of isoflurane as it appeared in 1983. Professor Conway presents a factual account of low flow and closed systems which is refreshingly devoid of evangelical fervour. There are useful chapters on halothane-induced arrhythmias and inhalation anaesthesia for cardiovascular surgery. Most of the remaining chapters are concerned with toxicity, and the editor contributes a well balanced account of the potential hazard from waste gases, including a preview of the Epistat survey. Dr Baden gives a valuable review of studies of carcinogenicity, mutagenicity and teratogenicity, fields in which he has contributed so much. Dr Brodsky presents an excellent account of the new aspects of the toxicity of nitrous oxide. Nephrotoxicity is handled by the editor and hepatoxicity by Dr Van Dyke, both chapters being lucid and authoritative.

Overall, this book is well produced and a pleasure to read. One especially appreciates English spelling in a book edited by an American! The index is poor, but the clarity of layout of the chapters makes it easy to locate a particular subject. Both topics and authors have been well chosen and the book will be an invaluable reference source for some years to come. This is a book that many anaesthetists will want to buy for their own collections.

J. F. Nunn

Physiology for the Anesthesiologist (2nd Edn). By Nishan Goudsouzian and Agop Karamanian. Published (1984) by Appleton–Century–Crofts, Norwalk, Connecticut. Pp. viii+482; indexed; illustrated. Price £37.60.

This compact (23 × 16 × 3 cm) handsomly bound volume cost just under £40 at December 1984 $/£ exchange rates. Written by anaesthetists for anaesthetists, it has the expected predominant emphasis on circulation plus respiration (about 60% of the book) with shorter sections on the nervous, endocrine and renal/fluid systems. The book is divided into 30 chapters, many of about 10 pages—suitable for digestion at a fairly brief sitting, or perhaps over a meal. The authors say in their preface, "we have designed this book to be especially helpful to the beginning or practicing anesthesiologist or anaesthetist who wishes to refresh his or her memory." Perhaps it is difficult to cater for such a wide spectrum and the book is probably more for refreshment than for beginning. It is written in a concise and quite concentrated style (reminds me of Ganong) and is well-referenced, around 20 per chapter, with 72 references after the chapter on the spinal cord, spinal nerves and pain. Most chapters have a strong and practical anaesthetic application, for example: Anaesthetics and myocardial function; Effect of anaesthetic agents on cardiac output; Impaired oxygenation during anesthesia and the postoperative period; Ventilators; Pain relief.

Most reviewers manage to come up with a few niggling points of criticism to show that at least they have read the pages concerned, and I am no exception. For example, the table on page 124 shows that exercise can cause a 12-fold increase in cardiac index (that is, output), with a 3- to 4-fold increase in minute ventilation—a curious inversion. Again, page 58: "The diastolic pressure usually corresponds better to the point at which the sounds become muffled (Phase IV) than to that at which they become silent". This is rather against current trends of thought. The detailed table of average values for "ventilatory function tests", page 224, with for example vital capacity 4800 ml, residual volume 1200 ml, FEV 83%, oxygen consumption 240 ml min^{-1} might be softened by more discussion of the factors—size, age, sex—which make for the wide range of normality. As is to be expected in an American book, S.I. units are conspicuous by their absence, with mm Hg retained for the blood-gases and mg/dl for calcium concentrations.

As an applied physiologist I enjoy meeting anaesthetists in the Primary/Part 2 F.F.A. exams and I enjoyed this book in the same spirit—anaesthesia is *par excellence* applied physiology. I recommend this book to all interested in the subject of its title, provided their basic physiology is not too rusty, and provided they can raise the necessary cash. Thus, the abler student and his/her tutor could find it a stimulating guide to the subject.

W. F. M. Wallace

Mortality in Anaesthesia. Edited by M. D. Vickers and J. N. Lunn. Published (1983) by Springer-Verlag. Pp. 341; illustrated. Price $48.20.

This volume, published entirely in English, comprises abstracts of papers presented at the third meeting of the European Academy of Anaesthesiology held in Paris in September 1982. The main topics of that meeting, notably complications and mortality associated with anaesthesia, occupy approximately 30% of the book and the remainder is devoted to abstracts of free papers. In addition, there is a four page precis of the Guest Lecture by Professor Albe-Fessard on the possible role of the two central projection areas of the spinothalamic inflow in the appreciation of pain, and a six-page summary of a somewhat inconclusive debate on the merits and demerits of i.v. and inhalation agents for promoting general anaesthesia.

There has been muted but widespread commment of late on the dubious value of publishing abstracts of papers which have not undergone peer review. Nonetheless, this volume and its predecessors serve a useful role in recording research in progress in anaesthetic centres in Europe, and draw to the attention of those whose sole language is English that there is a considerable amount of valuable anaesthetic research undertaken in Continental Europe. However, the greatest value of the book will be found in the section devoted to mortality in anaesthesia. Although each of these abstracts is relatively short, with details of methodology too brief to permit critical appraisal, nonetheless here is the most comprehensive collection so far compiled, of anaesthetic mortality studies including the British and French mortality studies, paediatric anaesthetic mortality in Paris, anaesthetic mortality and pulmonary function in Stockholm, cardiac deaths associated with anaesthesia and surgery (including a synopsis of the well-known studies from the U.S.A.) and medico-legal problems of anaesthetic death in five European countries.

This volume can be recommended for those seeking a broad background to the topic of anaesthetic mortality, and it also forms an excellent starting point and source of references for those wishing to research this topic in depth. Since no aspect of anaesthesia can surpass mortality in importance, it follows that most libraries would be well advised to obtain a copy.

G. Smith

Current Topics in Pain Research and Therapy. Proceedings of the International Symposium on Pain. Edited by T. Yokota and R. Dubner. Published by Excerpta Medica. Pp. 314; indexed; illustrated. Price $70.20.

At first glance this book looks like the typical Congress Abstract: a rather disjointed collection of papers with the contributions suffering badly from translation and editing. To a certain extent this holds true, but with names like Boas, Bond, Bonica, Lipton, Melsack, Nathan, and Wall amongst its contributors, chronic pain enthusiasts will be compelled to read on. When they have read this book they will, I think, find that they are well satisfied with the contents of this particular Congress Report—if not with its presentation, which suffers from numerous spelling errors and a variety of type-faces.

The book has been divided into five sections, I presume for convenience in referring to the diverse subject matter that a book on pain must contain. However, it makes nonsense of this process if the titles of the papers in the various sections bear little or no relationship to each other. For instance the paper on "The current status on post-operative pain therapy" and the paper entitled "Plasticity of central connections induced by either increased or by decreased afferent inputs" would probably be better in the sections titled "Clinical Problems of Pain" and "Neurophysiology of Pain", respectively, rather than being lumped together in the section entitled "Special Considerations on Pain". However, this muddle detracts only a little from the contents, which provide information on some entertaining experimental techniques in animals and (almost) in man; some good descriptions of practical clinical techniques; reviews of the more recent theoretical considerations in the anatomy and physiology of pain, and illustrations on the state of the art in various specialized pain fields.

Although, perhaps, one would tend to regard it as a book on Chronic Pain it is good to see a review on postoperative pain included, even if reading it reminds one that there are still too many operating departments in this country that do not have the facilities to provide postoperative pain relief of the highest quality. Overall, the book is a useful one for the anaesthetic or pain clinic library. It also has an excellent array of references and I, for one, am grateful for my copy.

K. M. Rogers

The Electroencephalogram in Anesthesia. Fundamentals, Practical Applications, Examples. By I. Pilchmayr, U. Lips and H. Kunkel (translated from the German by E. Bonatz and T. Masyk-Iversen). Published (1984) by Springer-Verlag, Berlin, Heidelberg, New York, Tokyo. Illustrated. Price DM98 (approx. US $35.70; £28.00).

The authors have set out to cover the fundamentals and practical applications of electroencephalography (EEG) in anaesthetic practice and to provide examples from their clinical experience in 1500 patients. The use of EEG to aid management of anaesthesia was well-established in the 1940s. Several machines were developed for automated delivery of anaesthetic agents based upon feed-back loops from the EEG. They fell into disuse as changing techniques made deep anaesthesia unnecessary and the dose-related EEG scales irrelevant. The more recent advent of several short-acting agents for total anaesthesia has led to a reappraisal of intra-operative EEG monitoring. Although now used primarily to give informed control of anaesthetic depth to the anaesthetist, it may also be a baseline against which complications potentially damaging to the brain can be recognized immediately.

For the routine application of EEG during anaesthesia to be a practical proposition, it is implicit that special data reduction and display techniques will be needed. After a useful and pithy historical review, the authors concentrate upon a single method, the compressed spectral array (CSA) based upon Fast Fourier Transforms. This gives series of sequential "plastic spectral mountains". Each "mountain" represents the electrical power at a particular frequency averaged over a chosen period of seconds or minutes and updated at regular intervals. The voluminous patterns of the EEG are converted to the more compact but equally complex and mysterious pattern of the CSA; they still present considerable measurement and interpretive problems for the observer. Thus, a comprehensive atlas of CSA patterns with indication of the related conventional EEG features and tabulation of effects of various doses is most welcome. The authors' great experience makes it possible for them to suggest that each agent produces an easily recognizable CSA pattern. Those with less grasp of the technique will probably find this hard to see. Indeed, mysteriously, the patterns shown from two different parts of the head often look more diverse than those from two different drugs. Other points of criticism are the extrapolation of Guedel's original planes of anaesthesia to halothane and the neurophysiological scales based rather arbitarily upon EEG frequency content alone (ignoring features such as pain responses as indicators that anaesthesia is too light and burst suppression patterns or electrical silence suggesting it is too deep). The weakest, and somewhat skimped, areas are those concerning operative complications and intensive care. Anaesthetic colleagues considered that the EEG methods were too complicated for routine clinical use and the book too specialized for the F.F.A. A biomedical engineer involved in surgical monitoring found it insufficiently practical and too biased in favour of CSA, which has many limitations compared with other EEG monitoring methods.

Such criticisms apart, the authors' immense work in documenting the effects of a large range of inhalation and i.v. anaesthetics, myoneural blocking agents and analgesics is of great value. The book is well set out, compact and agreeable to use. It will undoubtedly be widely referred to by the increasing number of workers venturing into this important area in order to improve their anaesthetic practice.

Pamela F. Prior

Anaesthesia: Safety for All. Edited by Q. J. Gomey, L. M. Egay and M. F. de la Cruz-Odi. Published (1984) by Excerpta Medica, International Congress Series 637. Pp. 650; indexed; illustrated. Price $130.75.

When Alexander the Great was young, his mother would put him in front of a mirror and say: "Son, today the mirror—tomorrow the world." Heady stuff for the introduction to any anaesthetic textbook—but this is no ordinary anaesthetic textbook. It contains some of the proceedings of the 8th World Congress of Anaesthesiologists held in Manila, January 22–28, 1984 and the aim of its publication is "to make available the highest standards of anaesthesia to all people of the world."

The book contains a summary (presumably) of five Plenary Lectures and between two and six contributions towards each of 22 Symposia. A comprehensive review of such a work would obviously be almost as long as the text itself and certainly this review is already almost as long as some of the contributions. As one might expect, the quality within ranges from excellent to less than useful.

The summaries of the Plenary Lectures are excellent and in particular I enjoyed the ones on toxicity of inhalation anaesthetics and pulmonary problems in anaesthesia. The other subjects include anaesthesia and brain function, inhalation anaesthetics and ethics in medicine. The titles of the Symposia reach far and wide into the different subspecialties within anaesthesia, for example pain relief in labour, high risk obstetrics, anaesthetic apparatus, monitoring and paediatric, cardiovascular and neurosurgical anaesthesia. Some space is devoted to the geriatric patient, critical care medicine, multiple injuries and of course education, training and manpower.

I believe some attempt should have been made to group related subjects together in the book, and I cannot understand why this was not done. I think that Symposia with titles such as isoflurane or neuromuscular blocking drugs are available in a better and more comprehensive form in other texts. The book is, of course, a collection of essays of varying length, typescript, reference style and illustration. In most essays there are no illustrations.

Perhaps all these flaws are inevitable in such a book, but I do not believe they are. No doubt the contributors will want to own a copy as a memory of the congress, but I cannot imagine who else will buy it. For those anaesthetists who did not attend the Congress, this book is of interest to tell us what we missed—although most of the information is probably available elsewhere.

Walter S. Nimmo

A Practice of Anaesthesia (5th Edn). Edited by H. C. Churchill-Davidson. Published (1984) by Lloyd-Luke (Medical Books) Ltd. Pp. 1200; indexed; illustrated. Price £50.00.

A few years ago while I was a pre-registration House Officer about to begin my first job in anaesthesia, I went to the local medical book shop and asked for the "best textbook of anaesthesia available". The bookseller sold me Wylie and Churchill-Davidson's 3rd Edition at a cost of £12. I read it, enjoyed it and passed the F.F.A.R.C.S. Therefore, I have a soft spot for this book which, by any standard, has been successful, having gone from the 1st edition in 1959 to the 5th edition in 1984 with four reprints also to its credit.

The most important changes from the 4th edition—which appeared in 1978, are the introduction of chapters on intensive therapy and anaesthesia for special situations. However, many of the original chapters have been completely rewritten by authors new to the team and the layout and reference style of the book has changed. Dr Churchill-Davidson now has 21 associate editors and three assistant editors writing a text of 45 chapters in eight sections. For the few people unfamiliar with the book, the sections are entitled: The Respiratory System, The Cardiovascular System, The Nervous System, The Metabolic, Digestive and Excretory Systems, The Endocrine System, The Reproductive System, Special Situations and History. In addition there are two appendices, entitled Care and Sterilisation of Anaesthetic Equipment and Useful Facts.

Section titles do not always give a clear indication of the chapter titles, however, and general pharmacological principles appear in the nervous system while paediatric anaesthesia is linked with the reproductive system. By and large the book is amazingly comprehensive, with very few serious omissions. Also, knowing the time it must have taken to write, it is remarkably contemporary. There are quite a few references from 1983 in the text.

The book is well produced and the format does make it easy to read. Many of the pictures and illustrations are old and I think that maybe the concept of a book such as this is a bit old too. There are many more competitors now than there were when I bought the 3rd edition. It is expensive and not just right for any part of the new F.F.A.R.C.S.: I do not think it will be very popular with trainees. However, anaesthesia is about life and not just training and examinations. This books is an educating text in the real sense of the word. I still like it!

Walter S. Nimmo

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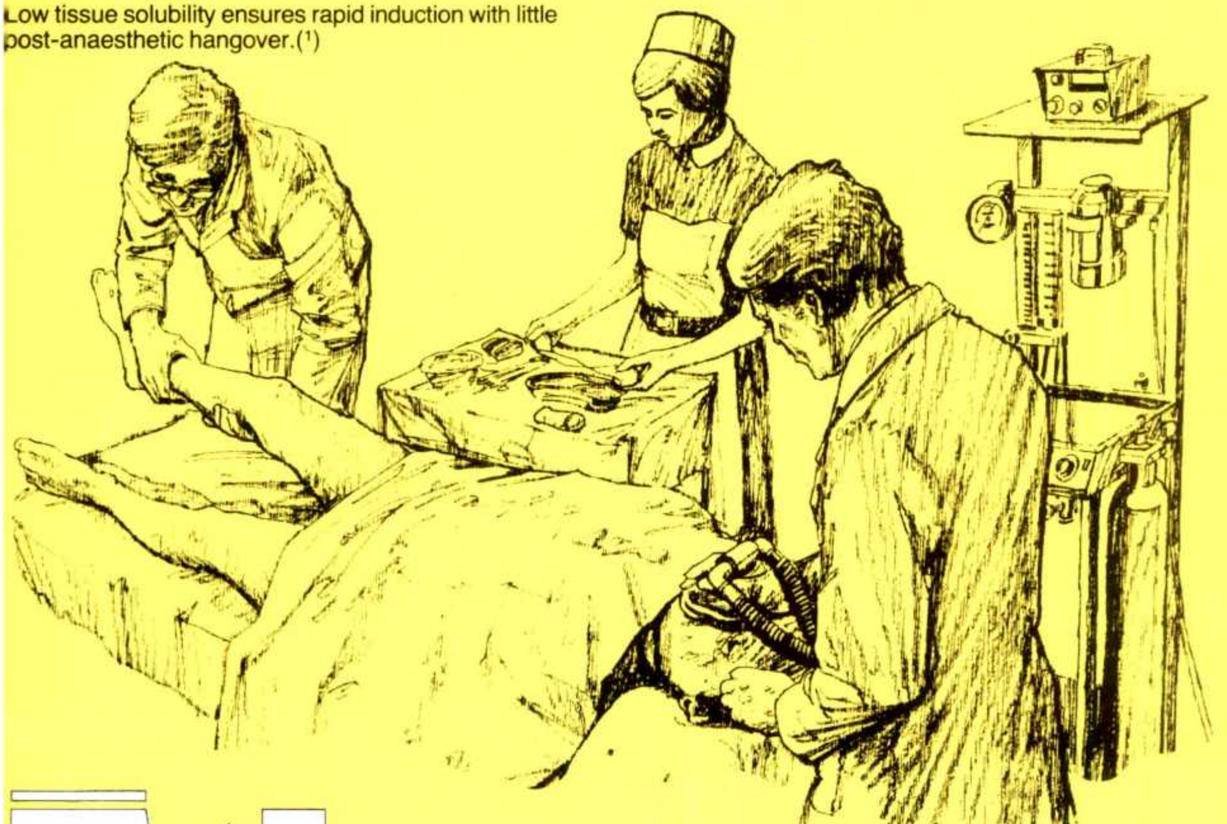

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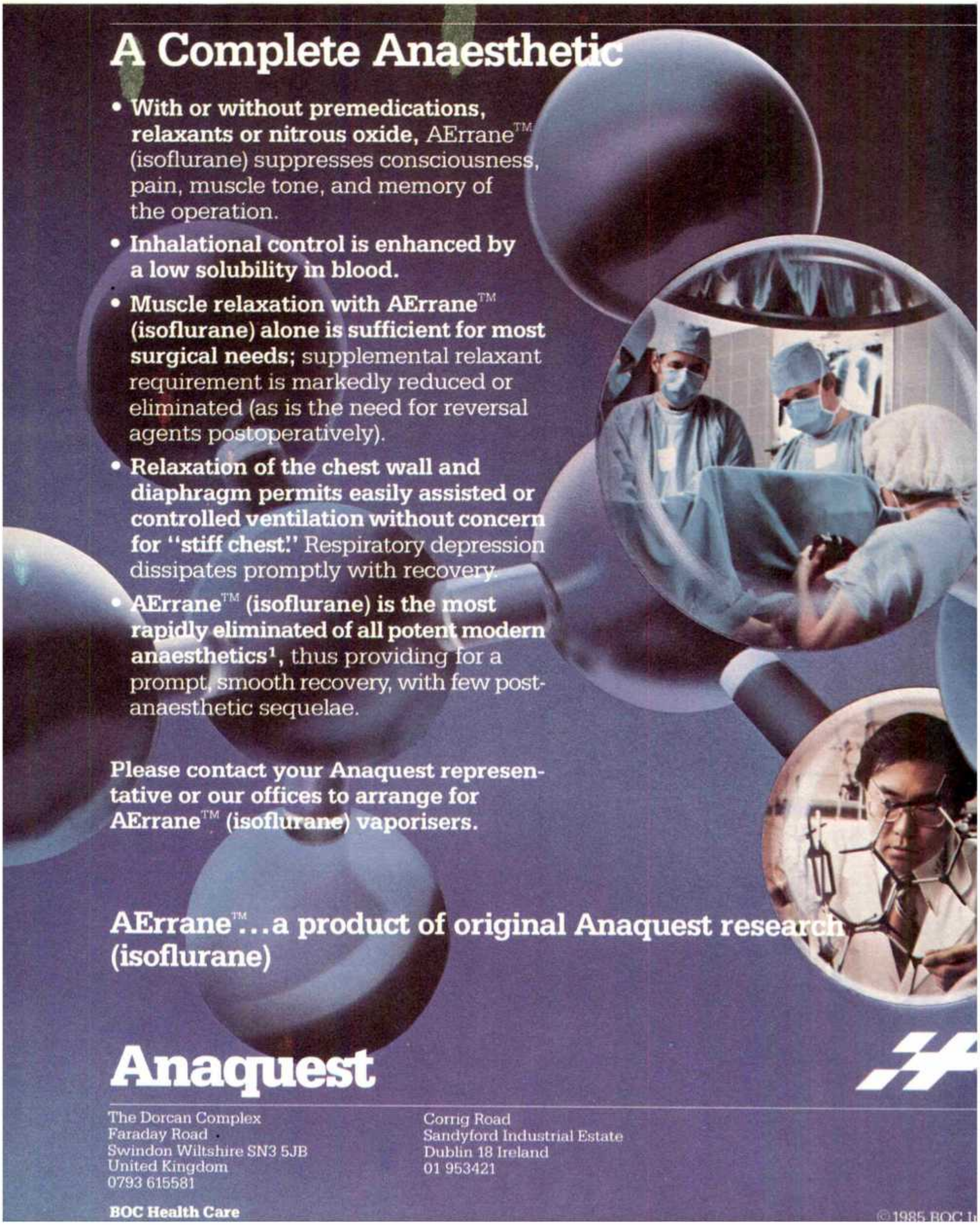

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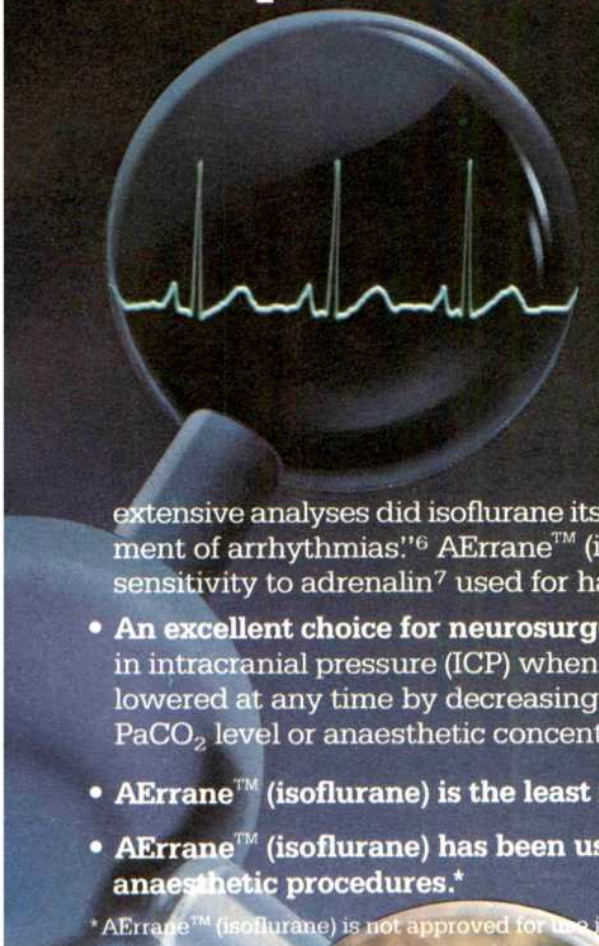

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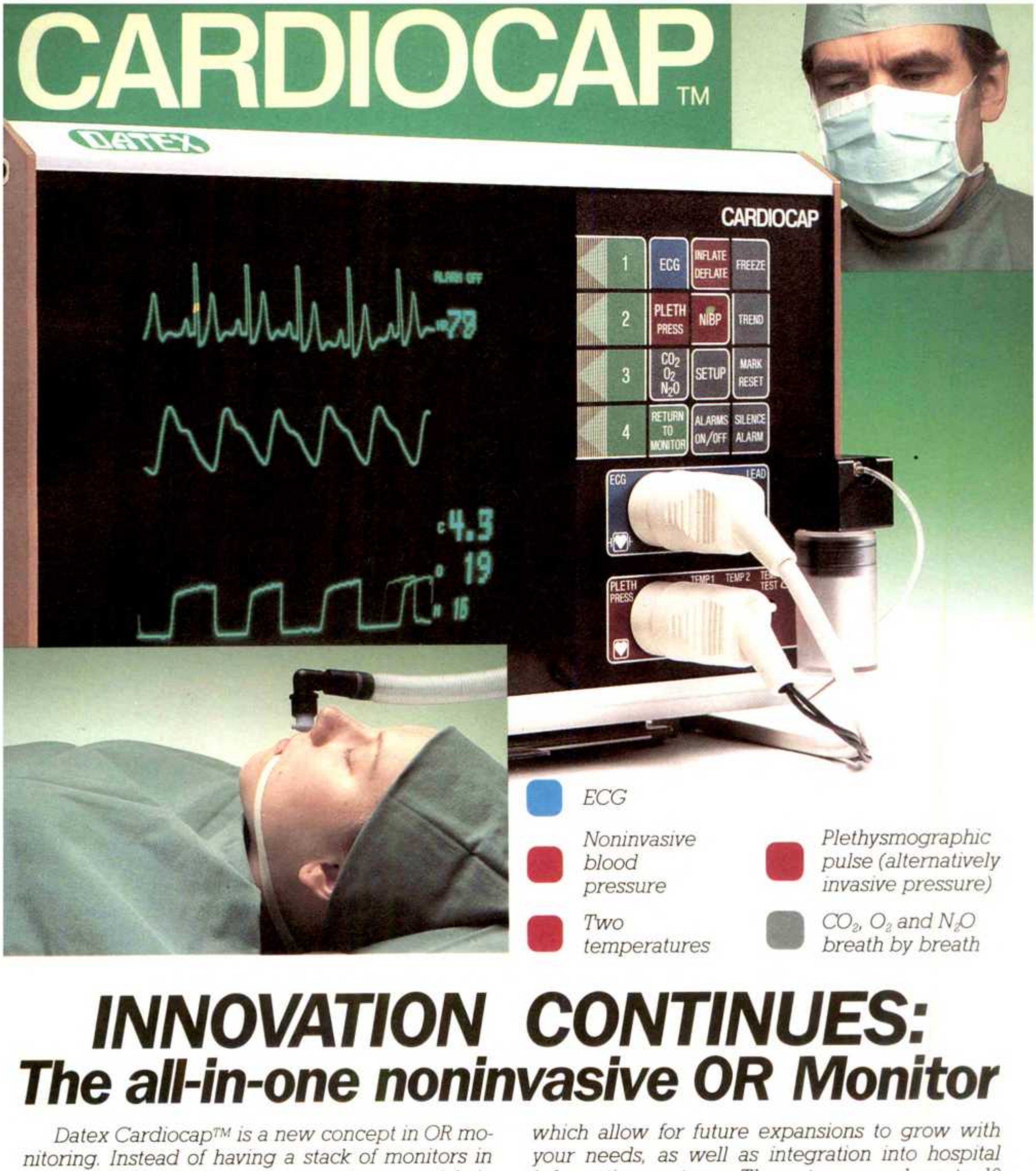

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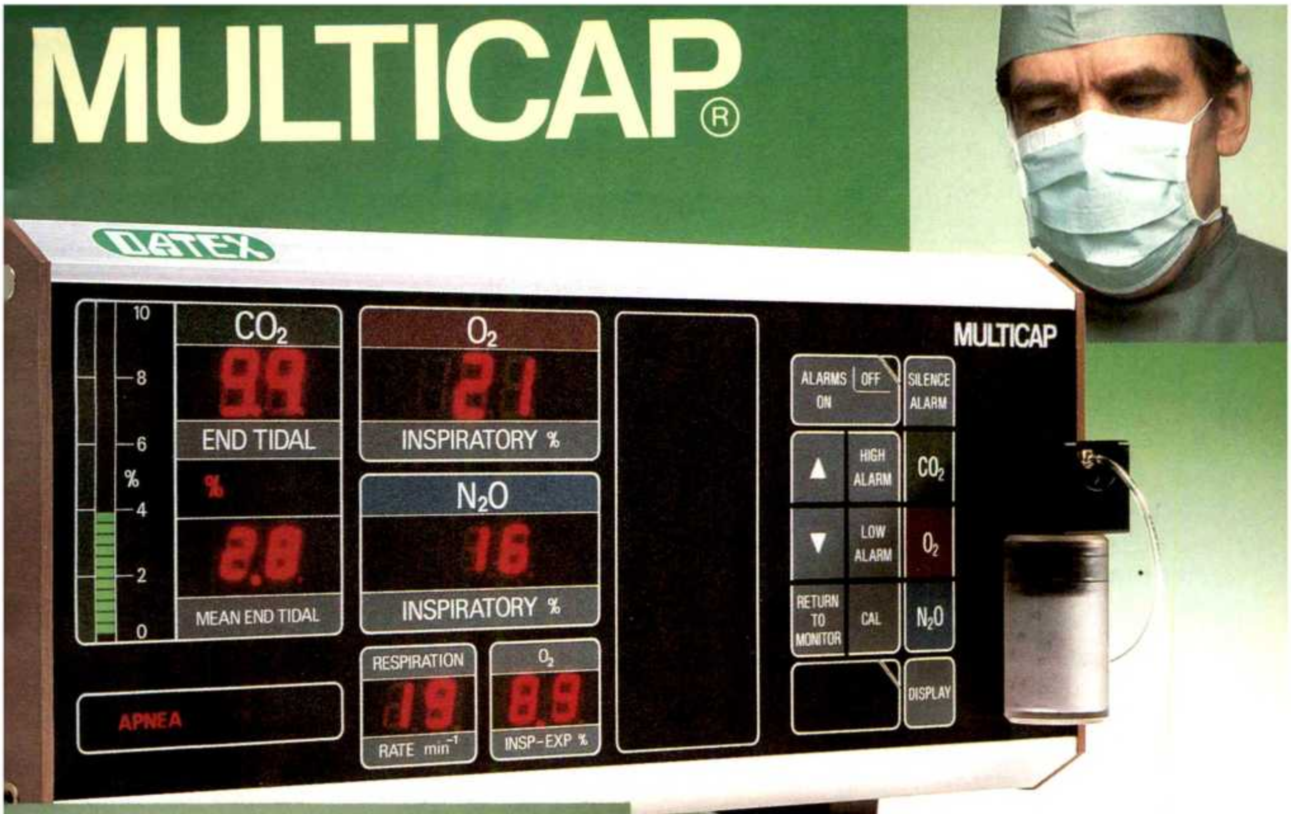

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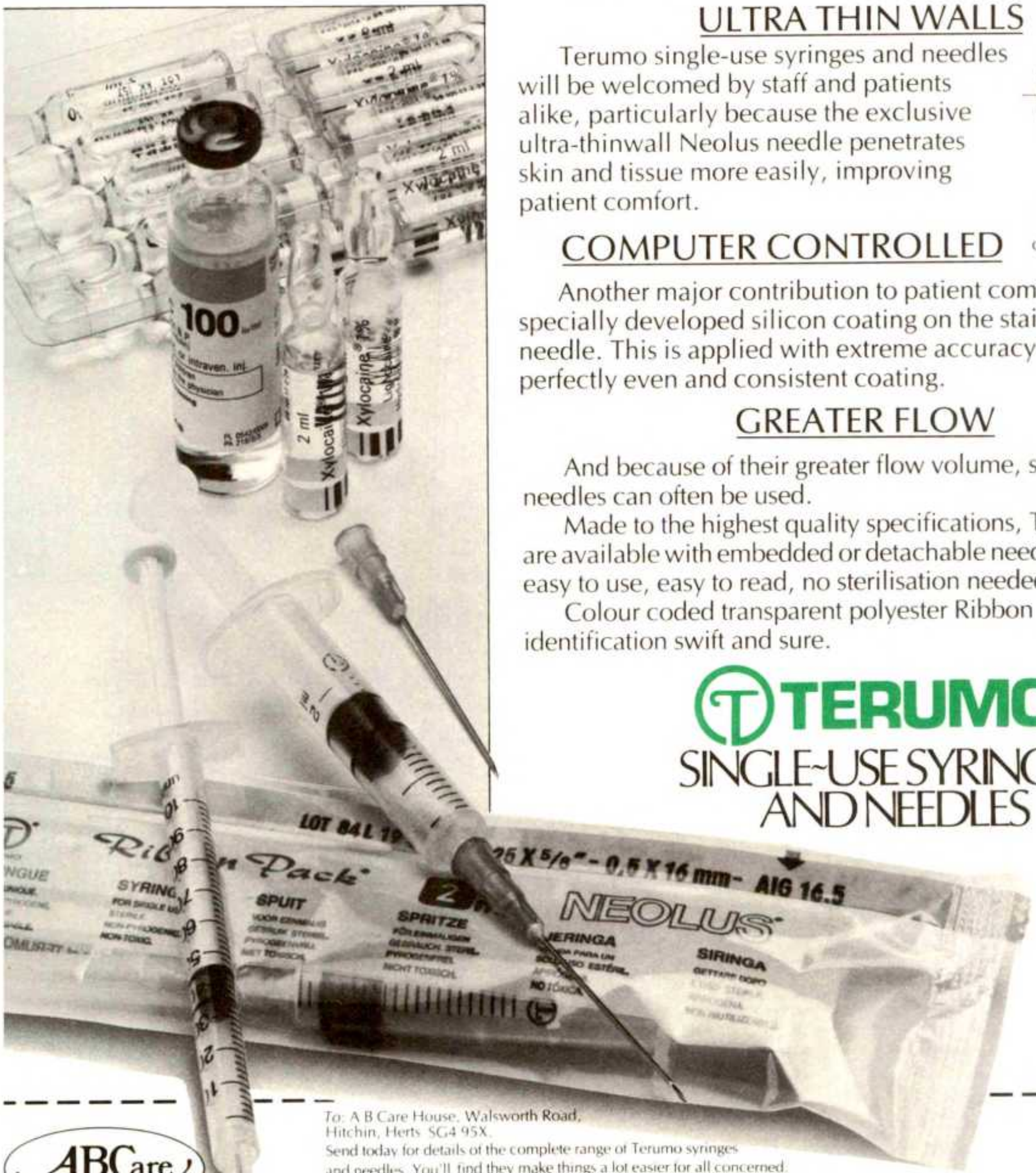

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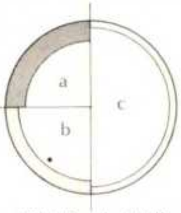

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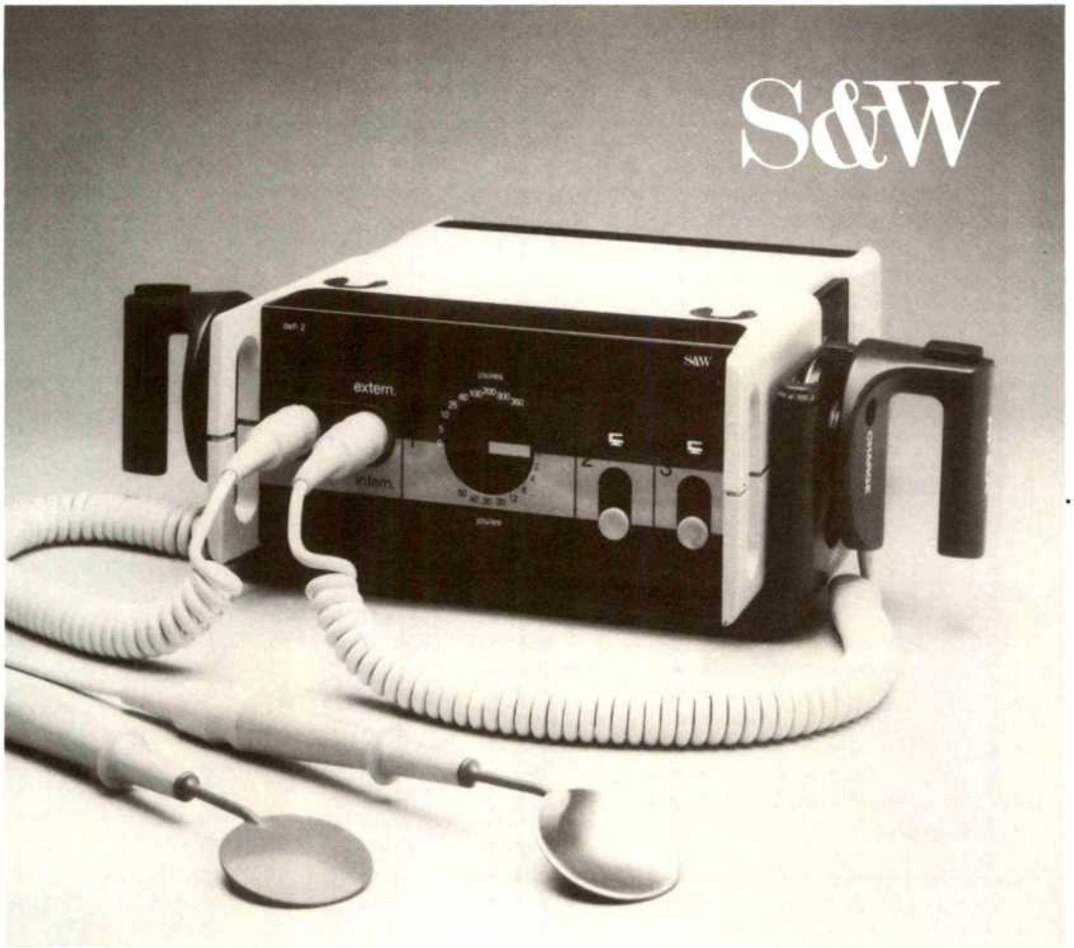

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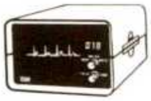
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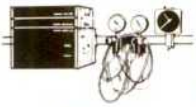
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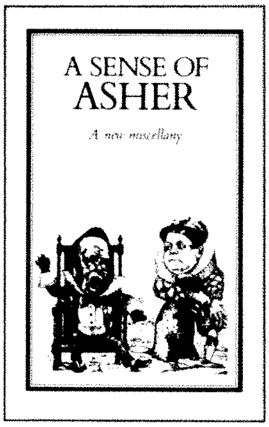

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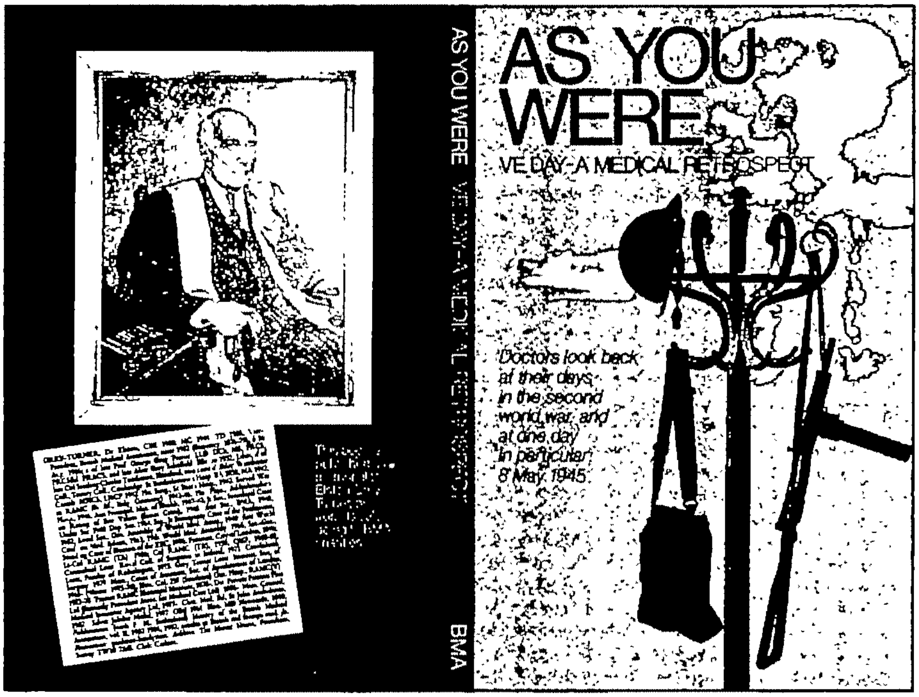
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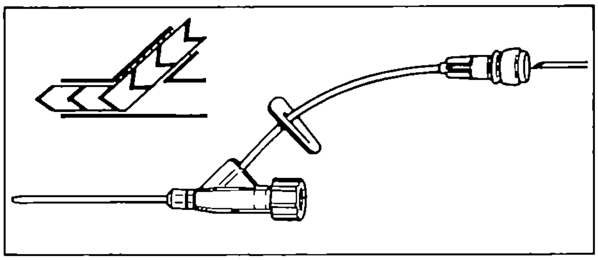

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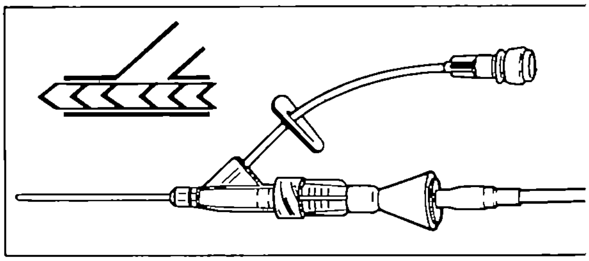

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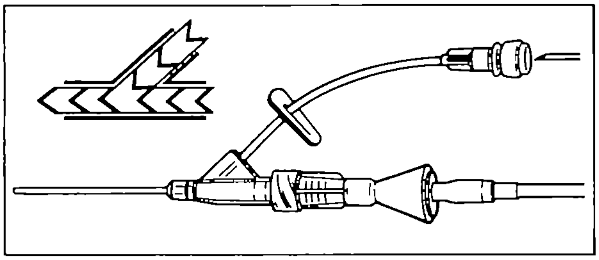

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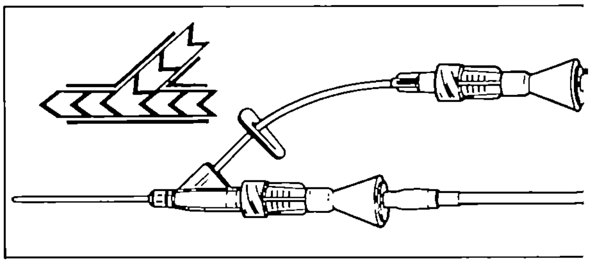

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REFERENCES: 1. AYLIFFE, G. LOWBURY, E.J. *et al*, Intravenous Infusions. *Control of Hospital Infection Handbook*
2. KELSEY, M.C. and GOSLING, M. *J. Hosp. Inf.* 1984; 5, 313.

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EFFICACY OF THE EXTRADURAL ADMINISTRATION OF LOFENTANIL, BUPRENORPHINE OR SALINE IN THE MANAGEMENT OF POSTOPERATIVE PAIN

A Double-blind Study

P. BILSBACK, G. ROLLY AND O. TAMPUBOLON

SUMMARY

Sixty postoperative orthopaedic patients were randomly assigned to three equal groups to study, in a double-blind fashion, the analgesic effects, durations of action and side effects of the extradural administration of lofentanil 5 μg, buprenorphine 0.3 mg or physiological saline. No systemic analgesics were given before, during or after surgery, and all the patients had operations on the lower extremities under extradural analgesia (lignocaine and bupivacaine). Eleven millilitre of the test drug was injected at T12–L1 as soon as pain occurred in the postoperative period. We observed a long duration of action and a marked analgesic effect with lofentanil, a shorter duration of action and less pain suppression with buprenorphine and a rather marked placebo effect after saline. The only side effect noticed in this study was drowsiness in three patients in the lofentanil group and in two patients in the buprenorphine group.

Shortly after the demonstration of the presence of opioid receptors in the substantia gelatinosa (Cavillo, Henry and Neuman, 1974; Perth, Kuhar and Snyder, 1976; Kitahata et al., 1977; Snyder, 1977), the use of intrathecal and extradural opioids in the management of chronic and acute pain was reported (Yaksh and Rudy, 1976, 1977; Yaksh et al., 1976; Wang, 1977; Wang, Nauss and Thomas, 1979). However, the initial enthusiasm for the use of these techniques in clinical practice was soon tempered by reports of adverse reactions, such as pruritus, vomiting, urinary retention (Reiz and Westberg, 1980; Samii, Chauvin and Viars, 1981), and delayed respiratory depression (Boas, 1980; Christensen, 1980; Davies, Tolhurst-Cleaver and James, 1980; Reiz and Westberg, 1980).

Most of these clinical studies were open and uncontrolled; different doses and different drugs were used and injected at different segmental levels, so that seldom could appropriate comparisons be made. The present study compared the analgesic efficacy and duration of action of two extradurally administered long-acting analgesics, lofentanil and buprenorphine, and compared the findings with those following the administration of physiological saline.

PATIENTS AND METHODS

Choice of analgesic

Although several opioids, agonists as well as agonists/antagonists, have been administered by the extradural route, we were interested in finding a long-acting drug that might be devoid of side effects.

Lofentanil is a new fentanyl derivative. In studies in animals it was 20 times more potent than fentanyl and approximately 6000 times more potent than morphine. Its exceptionally long duration of action (> 24 h) appears to be attributable to persistent occupation of opiate receptor sites (Gommeren and Leysen, 1982). Although lofentanil has been used previously via the extradural route to suppress pain, the results were controversial, and drowsiness and nausea were reported (A. Van Steenberge, personal communication). Before starting the present double-blind study, we performed an open pilot study with lofentanil in 13 patients with postoperative pain after ortho-

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TABLE I. *Sex, age, weight and height of the patients (mean ± SEM; range in parentheses). ns = Not significant*

	Placebo ($n = 20$)	Buprenorphine ($n = 20$)	Lofentanil ($n = 20$)	Kruskal–Wallis three-sample test
Sex (M/F)	13/7	13/7	15/5	
Age (yr)	38.4±3.0	35.5±3.6	34.8±3.7	ns
	(20–63)	(19–68)	(19–68)	
Weight (kg)	71.4±2.2	71.4±1.9	70.1±2.0	ns
Height (cm)	170.2±1.8	173.1±1.8	171.5±1.7	ns

paedic surgery. Lofentanil 5 µg in saline 11 ml was administered extradurally (L3–L4). In eight of the 13 patients, analgesia was good and lasted for at least 72 h. In one patient pain recurred after 20 h and in two other patients pain relief was moderately good. In two patients lofentanil was without noticeable effect. All the patients seemed to become sleepy after the injection, but could be aroused easily. There were no other side effects.

Buprenorphine was chosen as the reference drug for the present study since it has been used frequently via the extradural route (Lecron, Levy and Toppet-Balatoni, 1980; Rondomanska, 1980; Carl, Crawford and Wolfe, 1981; Kierkegaard et al., 1981; Zenz et al., 1981).

Patients and technique

Sixty adult patients with postoperative pain after orthopaedic surgery performed under extradural anaesthesia, were selected. The study had been approved by the ethics committee of the Academic Hospital and the patients gave informed consent.

Anaesthesia for the surgical procedure was performed with 2% lignocaine 10 ml with adrenaline 1:80000 mixed with 0.5% plain bupivacaine 10 ml and administered via an extradural catheter inserted at the third lumbar space. Immediately thereafter, a second catheter was inserted three spaces higher and advanced cephalad for 1.5 cm.

Coded 1-ml ampoules containing lofentanil 5 µg (L), buprenorphine 0.3 mg (B) or saline (S) were diluted with saline to a standard volume of 11 ml. As soon as pain occurred in the early postoperative period, patients received the trial drug via the most cephalad catheter. The patients were randomly divided into three groups of 20. Pain intensity as reported by the patients, systolic and diastolic arterial pressures, and heart and respiratory rates were recorded before administration, and at 10, 20, 30, 40 and 60 min and 2, 3, 4, 6, 10, 12, 20, 30, 40 and 72 h after injection. Side effects were sought and recorded. The degree of pain was evaluated using the following scores: no pain, mild pain, moderate pain, severe pain or very severe pain.

If pain relief was unsatisfactory (very severe, severe or moderate pain) 40 min after injection, 0.25% bupivacaine 15 ml with adrenaline 1:200000 was given via the lower catheter, the result was coded as "no effect" and these patients were withdrawn from the study (early withdrawal). At that time, the two catheters were removed in all patients. If "unsatisfactory pain relief" was noted subsequently, the patient received pentazocine 45 mg i.m. and was withdrawn from the study at that point (late withdrawal).

Statistical analyses were by the Kruskal–Wallis test and $P < 0.05$ was considered significant.

RESULTS

The three groups of 20 patients were comparable for age, weight and height (table I). The distribution of the sites of operation is shown in table II. The time between the last injection of local anaesthetic during surgery and the injection of the trial drug was 259±16 min (mean±SEM) for L, 271±16 min for B and 274±28 min for S.

The distributions of the pain scores at the various times of assessment are shown in figures 1, 2 and 3.

TABLE II. *Site of operation*

	Placebo	Buprenorphine	Lofentanil
Hip	3	2	1
Femur	2	—	1
Knee	6	7	8
Tibia	8	8	8
Ankle	1	3	—
Foot	—	—	2
Total	20	20	20

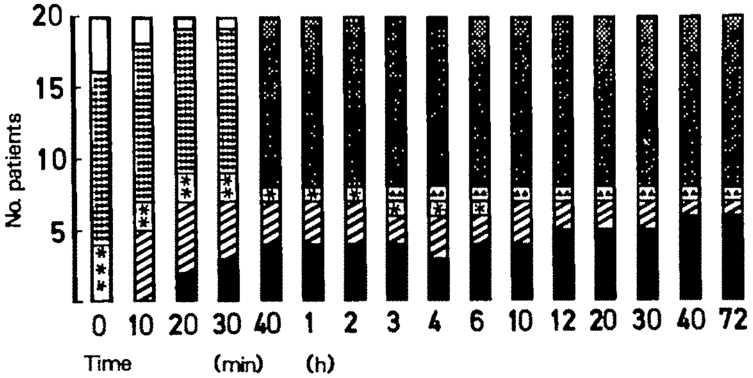

FIG. 1. Pain evaluation after placebo ($n = 20$). ■ = No pain; ▨ = mild pain; * = moderate pain; • = severe pain; ☐ = very severe pain; ▲ = unsatisfactory pain relief; stippling = no effect. (Key applies to figures 2, 3 also.)

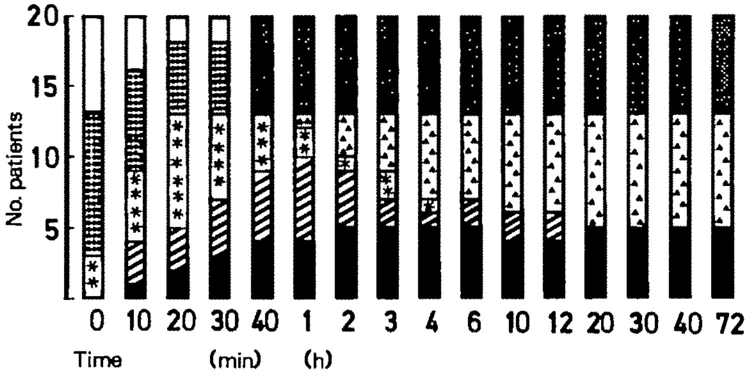

FIG. 2. Pain evaluation after buprenorphine ($n = 20$).

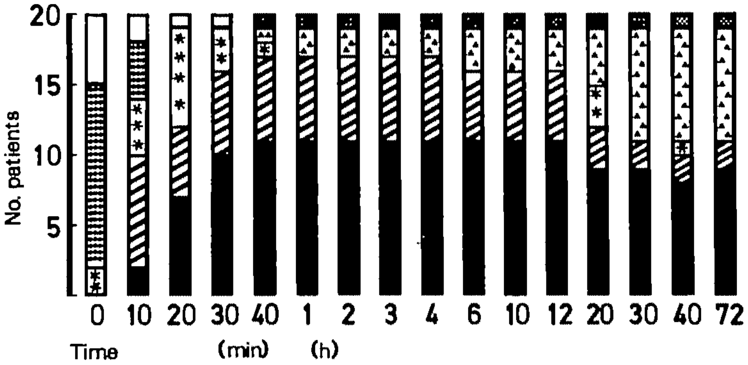

FIG. 3. Pain evaluation after lofentanil ($n = 20$).

TABLE III. *Cumulative numbers of patients with insufficient pain relief at different time intervals after injection* (n = 20 *in each group*)

	Time (min)		
	40	60	240
Placebo	12	12	13
Buprenorphine	7	9	13
Lofentanil	1	3	3

No statistical differences existed between the three groups immediately before the administration of the test drug. The onset of analgesia was observed generally between 10 and 20 min for lofentanil and buprenorphine, with a gradually increasing effect. At 40 min after injection, 12 (S), seven (B) and one (L) patients reported no effective pain relief (severe or very severe pain) and were excluded from the rest of the study (early withdrawal). Another patient (L) complained of unsatisfactory pain relief just after the extradural catheter had been removed, was given the i.m. analgesic and rated as unsatisfactory. The analysis of the cumulative numbers of patients reporting unsatisfactory or no pain relief (table III) is in favour of lofentanil (significant difference between S and L, and B and L).

At 12 h, seven (S), six (B) and 16 (L) patients and at 30 h seven (S), five (B) and 11 (L) patients still had mild or no pain, confirming the long duration of action of lofentanil. The differences in degree of pain between placebo and lofentanil and between buprenorphine and lofentanil were statistically significant at several time intervals (table IV), each time in favour of lofentanil. There were no significant differences between any groups after 30 h.

TABLE IV. *Statistical evaluation of pain evaluation before and after extradural administration* (*Mann–Whitney* U *test*)

	Before extradural	Time after extradural administration							
		20 min	40 min	1 h	3 h	6 h	12 h	20 h	30 h
Placebo *v.* lofentanil	0.598	0.007	0.003	0.006	0.004	0.008	0.017	0.057	0.239
Buprenorphine *v.* lofentanil	0.797	0.01	0.011	0.018	0.012	0.017	0.007	0.022	0.14
Buprenorphine *v.* Placebo	0.797	0.617	0.33	0.394	0.626	0.914	0.776	0.695	0.695

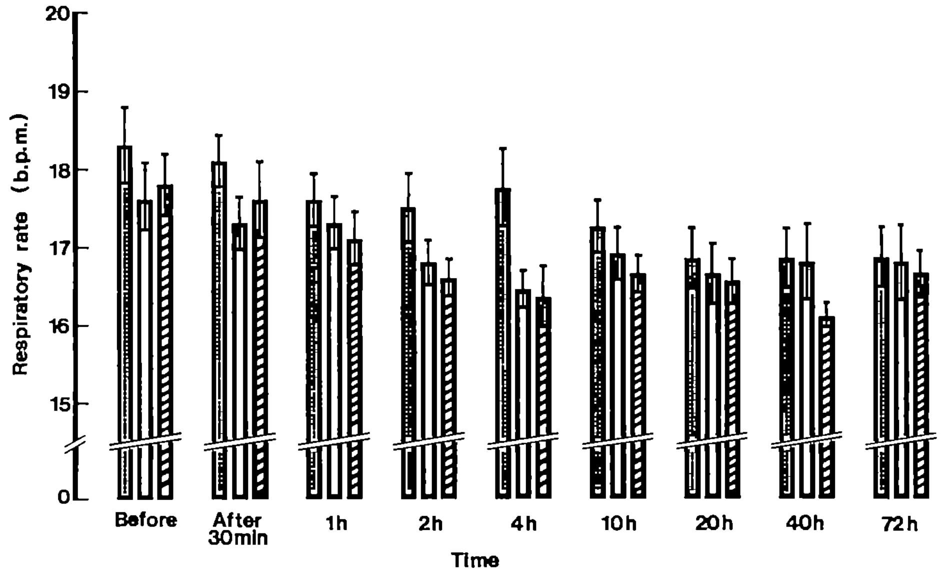

FIG. 4. Respiratory rate (mean ± SEM) after injection of placebo (dotted columns), buprenorphine (open columns) and lofentanil (cross-hatched columns) (*n* = 20 each).

TABLE V. *Side effects*

	Placebo ($n = 20$)	Buprenorphine ($n = 20$)	Lofentanil ($n = 20$)
Apnoea	0	0	0
Bradypnoea (< 16 b.p.m.)	0	0	1
Sleepiness	0	3	3
Sweating	0	1	0
Nausea	0	0	0
Vomiting	0	0	0
Pruritus	0	0	0
Urinary retention	0	0	0

No distinct cardiovascular or respiratory depression was noted at any time in the three groups. A transient period of bradypnoea (respiratory rate of 12 b.p.m.) lasting for 30 min occurred in one (L) patient, 90 min after injection. Mean respiratory rate was sometimes marginally higher in the S group than in the B and L groups (fig. 4), but no statistically significant differences were noted.

Side effects are shown in table V. Sleepiness was noticed in three (B) and three (L) patients and sweating in one (B) patient. Nausea, vomiting, pruritis or urinary retention were not observed in any of the patients.

DISCUSSION

The administration of opioids into the subarachnoid or extradural spaces for postoperative pain relief, has become popular in recent years in the management of postoperative pain. Of the two routes, extradural administration seems preferable, because of the lower risk of infection, the lack of postspinal headache and a lower incidence of side effects. Furthermore, incremental doses can be given via an indwelling catheter. However, most reports mention a failure rate of 10–20%. In an attempt to improve the success rate, the catheter was placed so that the trial drugs were placed at the level of T12–L1, the aim being to have the opioids injected as close as possible to the opioid receptors present in the substantia gelatinosa.

The most appropriate opioid for postoperative pain relief is still open to debate. Theoretically, any opioid except opium or piritramide, could be administered. To date the most widely used drug has been morphine, which produces effective, long-lasting analgesia, but at the expense of a high incidence of side effects.

The ideal drug should have the following characteristics:

high lipid solubility, inducing fast diffusion into the neural tissues, and little systemic absorption;

high molecular weight;

strong binding to receptor protein, thus producing a prolonged effect;

intense and prolonged intrinsic activity.

Theoretically, at least, the two drugs used in this study seemed to meet most of these characteristics.

Lofentanil had a rapid onset of action and a prolonged effect, and provided adequate pain relief in the majority of patients. No cardiovascular or respiratory depression occurred, confirming our preliminary open study (unpublished results). Three patients were drowsy, in contrast to our initial study in which all 13 patients were sleepy. Buprenorphine was less efficacious in the relief of pain, and its duration of action was shorter than might have been expected (Zenz et al., 1981), although unpredictable activity has been described after extradural administration (Kierkegaard et al., 1981). It is difficult to find a satisfactory explanation for the poorer suppression of pain, with buprenorphine. In most reports the site of injection was below L3–L4 and the drug was given after abdominal or gynaecological surgery. In the present study the drug was placed at T12–L1 and only orthopaedic patients were studied. Combining buprenorphine with a local anaesthetic might be more effective (Lecron, Levy and Toppet-Balatoni, 1980).

The placebo effect was marked in our study. Many studies have shown that about 30–35% of patients report marked pain relief after saline i.m. (Melzack, 1973), a figure close to the 25% found in the present study. McClure and colleagues (1980) compared extradural morphine with saline and found a significant decrease in mean pain score in the placebo group 20 min after injection. In addition, the extradural injection of saline 10 ml (at T10–T11) produced a placebo effect comparable to the analgesia provided by morphine 2 mg injected in the same volume in the lumbar area (Asari et al., 1981). Urbain and McKain (1978) demonstrated that saline 5–10 ml injected intrathecally produced segmental hypoaesthesia as well as partial sympathetic blockade. The relatively marked placebo effect after the extradural injection of saline, could, theoretically, be the result of the same modulation of pain perception which results from the intrathecal injection of saline.

Although itching, urinary retention, respiratory depression, nausea and vomiting are mentioned frequently in the literature, they were not observed in this series of patients. One reason might be the total omission of opioid drugs during the actual anaesthetic.

CONCLUSION

The extradural administration of lofentanil provided effective pain relief of long duration and was significantly better than after buprenorphine in these respects. Its use warrants further study. However, a word of caution about the unrestricted use of lofentanil might be appropriate for the time being, because of its very strong receptor-binding propefties and the lack of a suitable antagonist.

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POSTOPERATIVE ANALGESIA WITH DUROMORPH

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SUMMARY

The analgesic effects and bioavailability of a slow-release preparation of morphine (Duromorph) were studied in 12 patients with acute postoperative pain. Duromorph produced significant analgesia within 1–2 h of administration i.m., and there was a progressive decrease in the mean pain score for at least 8 h. None of the patients requested or received additional analgesia within 12 h, and the incidence of side-effects was similar to that associated with i.m. morphine. During the 8-h study, plasma concentrations of morphine slowly increased for 3 h, and then gradually declined. After 3 h, concentrations were invariably greater than those produced by conventional doses of morphine sulphate i.m. The study confirmed that Duromorph was an effective analgesic with a prolonged duration of action, which was suitable for the management of postoperative pain.

When morphine is used in the management of acute postoperative pain, the duration of effective analgesia is 4–6 h, and repeated parenteral administration is usually required (Denton and Beecher, 1949; Lasagna and Beecher, 1954; Nayman, 1979). Thus, long-acting preparations of morphine should have certain advantages, and should decrease the frequency of injections i.m. Nevertheless, in practice they appear to be rarely used, and little is known of their effectiveness in the management of postoperative pain. In this study, we have assessed the analgesic effects and bioavailability of a slow-release preparation of morphine (Duromorph, Laboratories for Applied Biology) in patients with pain after elective orthopaedic or abdominal surgery.

PATIENTS AND METHODS

The study was approved by the Hospital Ethical Committee, and informed and written consent to the procedure was obtained from patients during the routine preoperative visit. Twelve patients of both sexes were studied (table I): all were free from cardiovascular, hepatic and renal disease, and were admitted to hospital for elective abdominal or orthopaedic procedures. None was concurrently receiving opioid analgesics, non-steroidal anti-inflammatory drugs or steroids.

Following premedication with a benzodiazepine, anaesthesia was induced by the administration of a barbiturate i.v., and maintained with nitrous oxide, and halothane or enflurane in oxygen, with or without the use of a neuromuscular blocking drug. No analgesics were administered during the operation. All patients were studied within 2 h of the completion of surgery (depending on the time of their initial request for analgesia). On complaining of postoperative pain, patients were given Duromorph 1.0 ml i.m. Duromorph is a microcrystalline preparation of morphine, containing morphine base 64 mg in 1.0 ml; approximately 3.0 mg is present as free morphine, and the remainder as crystals 50–250 μm in diameter, from which the drug is slowly released over 9–12 h.

All patients were assessed at 0, 1, 2, 3, 4, 5, 6, 7 and 8 h after the administration of Duromorph. A visual analogue scale (a 10-cm marked vertical line) was used and the patient was asked to mark the point between "no pain" and "pain as severe as it can be" which best represented their pain. Patients were also asked at these times about the presence or absence of unwanted effects. The nature of any adverse effect was recorded, and its severity graded on a 4-point rating scale (4 = very severe, 3 = severe, 2 = moderate, 1 = slight).

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TABLE I. *Characteristics of the patients studied*

Patient No.	Sex	Age (yr)	Weight (kg)	Operation
1	F	54	75	Cholecystectomy
2	M	41	66	Laminectomy
3	F	50	54	Vagotomy and pyloroplasty
4	F	56	60	Partial gastrectomy
5	F	49	66	Vagotomy and pyloroplasty
6	M	25	90	Discectomy
7	M	58	57	Resection of bowel
8	M	21	77	Vagotomy and pyloroplasty
9	M	61	73	Gastrectomy and splenectomy
10	M	29	73	Anterior repair of shoulder
11	M	36	74	Laminectomy
12	F	43	70	Laminectomy and discectomy

Blood samples (approximately 10 ml) were obtained at hourly intervals. After centrifugation, morphine was extracted from plasma and its concentration was measured by high pressure liquid chromatography (Svensson et al., 1982). This method separates the parent drug from its glucuronide metabolites, and specifically measures unchanged morphine in plasma.

RESULTS

Duromorph produced significant analgesia within 1–2 h of i.m. administration, and there was a progressive decrease in the mean pain score (as assessed by the visual analogue scale) during the 8 h of the study (fig. 1). The initial pain score decreased from 8.2 ± 0.6 to 3.9 ± 0.8 (mean ± SEM) between 0 and 4 h and then declined more slowly. At 8 h, the pain score was 3.1 ± 0.7 (mean ± SEM) (fig. 1). None of the patients requested or received additional analgesia within 12 h.

Before the administration of Duromorph, five of the 12 patients complained of slight, moderate or severe nausea, and the total side-effect score was 12 (table II). This was usually relieved by Duromorph, although this preparation was associ-

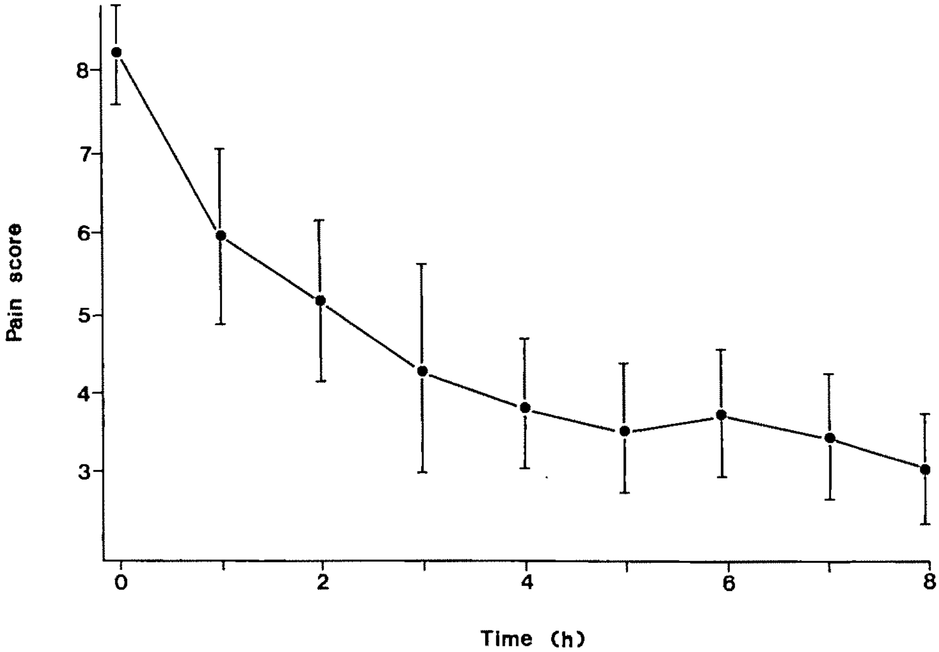

FIG. 1. Mean pain scores after i.m. injection of Duromorph. Bars represent SEM.

TABLE II. *Side-effects of Duromorph*

Time (h)	Total side-effect score in 12 patients			
	Nausea	Vomiting	Sedation	Dizziness
0	12	0	2	1
1	3	0	4	1
2	2	0	3	0
3	2	1	2	0
4	1	1	0	0
5	1	3	0	0
6	0	0	0	0
7	2	2	0	0
8	1	2	1	0

ated with characteristic side-effects in a small proportion of patients. Approximately 10–20% of patients complained of slight or moderate nausea or vomiting during the 8 h of the study. A similar proportion experienced some sedation during the first 4 h, although only two patients complained of slight dizziness (table II).

After Duromorph i.m., the plasma concentration of morphine progressively increased to a concentration of 64.5 ± 2.9 ng ml^{-1} (mean ± SEM) at 3 h, and then declined slowly (fig. 2). Between 4 and 8 h, morphine concentrations decreased by approximately 70% (from 51.4 ± 3.4 ng ml^{-1} to 16.3 ± 2.3 ng ml^{-1}). The bioavailability of Duromorph was assessed from the area under the plasma concentration–time curve between 0 and 8 h. In the patients studied, the bioavailability of Duromorph was 297.1 ± 3.8 ng ml^{-1} h^{-1} (mean ± SEM).

DISCUSSION

The administration of Duromorph was associated with a progressive decrease in the mean pain score for 8 h after surgery. The initial decrease in postoperative pain scores was similar to that produced by conventional morphine i.m. (Bell et al., 1985). A moderate degree of pain relief was invariably experienced within 1–2 h, and none of the patients requested or received additional analgesia for at least 12 h. These results suggest that Duromorph is a long-acting and effective analgesic that may be of considerable value in the control of acute postoperative pain. This conclusion is consistent with the results of other studies (Johnson, 1983). When Duromorph was administered 8-hourly in the management of postoperative pain, analgesia appeared to be better than that

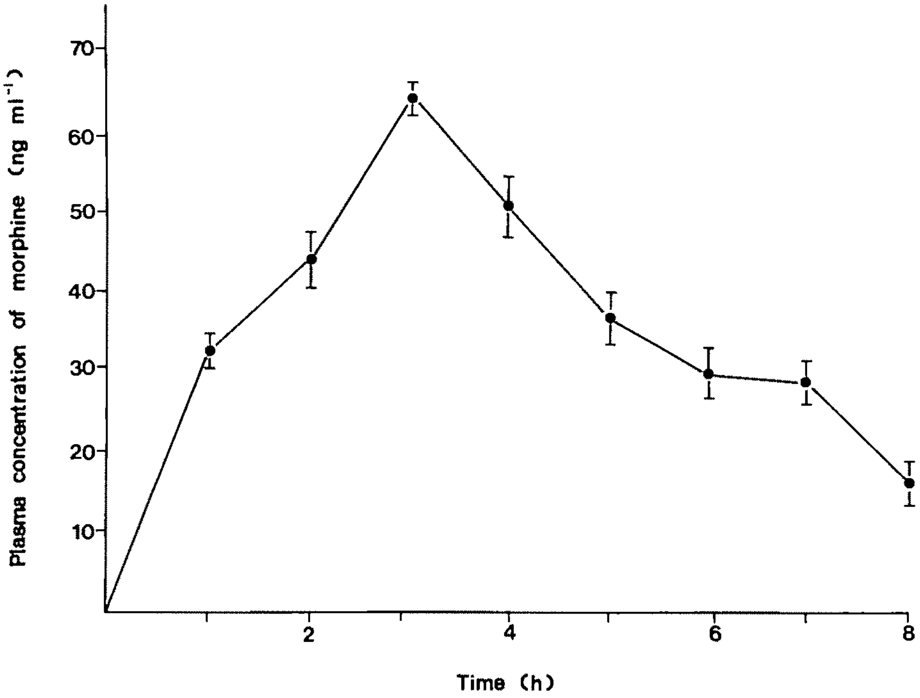

FIG. 2. Mean plasma concentration of morphine after i.m. injection of Duromorph. Bars represent SEM.

produced by standard methods. In addition nausea and vomiting were less common, and anti-emetic drugs were rarely required (Johnson, 1983). In the present study, 10–20% of patients complained of slight or moderate nausea or vomiting, although none was considered to require anti-emetic therapy. A similar proportion experienced some sedation. These results confirm that postoperative analgesia with Duromorph is not associated with an unacceptable incidence of undesirable side-effects.

After Duromorph i.m., plasma concentrations of morphine slowly increased for 3 h, and then gradually declined (from approximately 60 ng ml^{-1} to 16 ng ml^{-1}). Between 3 and 8 h, concentrations were invariably greater than those produced by conventional doses of morphine sulphate i.m. (Bell et al., 1985), and may reflect the slow absorption of the drug from the microcrystalline preparation. Plasma morphine concentrations were similar to or greater than the values that are usually associated with significant postoperative analgesia (Berkowitz et al., 1975; Nayman, 1979; Dahlström et al., 1982). Although previous studies suggested that the administration of Duromorph was associated with serum morphine concentrations of 60 ng ml^{-1} for at least 8 h (Johnson, 1983), these values were determined by radioimmunoassay. In these circumstances, cross reactions with the glucuronide metabolites of morphine may result in the overestimation of the unconjugated drug (Aherne, 1983; Vater et al., 1984). Analytical errors are particularly likely to arise when the concentration ratio of conjugated metabolites to unchanged morphine is more than 10:1 (Hanks and Aherne, 1985). Although definite evidence is not available, it is probable that these ratios are present after repeated doses of Duromorph i.m.

In the present study, the bioavailability of Duromorph, as defined by the area under the plasma concentration–time curve between 0 and 8 h, was 297.1 ± 3.8 ng ml^{-1} h^{-1}. In contrast, the bioavailability of morphine sulphate 13.3 mg i.m., when measured in comparable conditions, was 169.1 ± 4.5 ng ml^{-1} h^{-1} (Bell et al., 1985). These results suggest that the total bioavailability of Duromorph is approximately 75% greater than morphine i.m.; however, when compensation for the different amounts of morphine in the two preparations was made, the bioavailability of Duromorph was only 27% that of morphine sulphate. Clearly, the period of sampling used in this study did not adequately define or describe the bioavailability of Duromorph. Morphine may well be released slowly from the crystalline preparation for some considerable time (days or even weeks); in these conditions, cumulation of the drug might occur after frequent or repeated dosage of Duromorph. The present study was concerned only with the use of single doses of Duromorph. Nevertheless, when the drug was given 8-hourly for 40–48 h after surgery, there was no evidence of cumulation (Johnson, 1983).

When compared with other opioid analgesics, the lipid solubility of morphine is relatively low. Consequently, morphine equilibrates slowly with the CNS, and plasma concentrations of the drug after single doses may not be directly related to its analgesic effects (Yang et al., 1979; Hug et al., 1981). Nevertheless, after the injection of Duromorph, the presence of significant concentrations of morphine in plasma was associated with prolonged and enhanced analgesia. In these conditions, increased amounts of morphine may enter the CNS slowly, and produce analgesic effects for a considerable time after the drug has disappeared from the plasma.

In conclusion, this study shows that Duromorph is an effective analgesic with a prolonged duration of action. A single i.m. injection usually produces analgesia for at least 12 h, and plasma concentrations of morphine were usually greater than those produced by conventional doses of morphine sulphate i.m. Present views on analgesic drugs suggest that future advances may well depend on the use of currently available drugs in a more efficient manner (Utting and Smith, 1979). By decreasing the need for frequent i.m. injections, Duromorph may well represent progress in this direction.

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BACLOFEN PROLONGS THE ANALGESIC EFFECT OF FENTANYL IN MAN

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It has been shown that GABAergic compounds can potentiate opioid-induced analgesia (De Feudis, 1982) and that baclofen (β-(4-chloro-phenil)-γ-aminobutyric acid), possesses intrinsic analgesic activities in a variety of species (Levy and Proudfit, 1977). Thus, it seemed worthwhile to investigate the effects of baclofen in man during nitrous oxide–fentanyl anaesthesia in which fentanyl could be considered as the only variable affecting the control of pain.

SUMMARY

Pretreatment with baclofen prolonged the duration of fentanyl-induced analgesia from 18 to 30 min in patients undergoing neurosurgical anaesthesia (fentanyl plus nitrous oxide in oxygen). This observation is consistent with a potentiating effect of GABA on opioid analgesia.

PATIENTS AND METHODS

Three groups (10 patients each) undergoing transphenoidal hypophysectomy entered the study. The 30 patients (20 males), 25–60 years of age, and within 10% of their ideal body weight, were randomly assigned to one of the three groups. Mean (±SD) ages were 52 yr±6 for group 1, 46 yr±12 for group 2 and 46 yr±10 for group 3, and their mean weights were 70 kg±9, 67 kg±11 and 69 kg±10, respectively.

Patients in group 1 were pretreated with saline, those in group 2 with baclofen (Lioresal, Ciba-Geigy, Origgio, Italy) 0.6 mg kg^{-1} i.m. in four doses for 5 days; and those in group 3 received baclofen 0.6 mg kg^{-1} i.v. in 5% glucose 100 ml 45 min before the beginning of surgery. All the anaesthetics were conducted by the same anaesthetist (R.M.), who had participated in the planning of the trial, but was unaware of the specific test treatment received by the individual patient. Anaesthesia was maintained with 10% nitrous oxide in oxygen and analgesia was provided with subsequent administrations of fentanyl in single doses of 0.001 mg kg^{-1}. The intervals between the doses of fentanyl were variable and were used as a measure of the analgesic efficacy of the opioid. During surgery, several variables were monitored continuously: heart rate, arterial pressure, ECG, airway pressures, pupil size and evidence of lachrymation and sweating. Changes in these variables were used as criteria for the timing of the administrations of fentanyl. Fentanyl was administered when (there being no hypovolaeima) at least one of these variables, when observed at least 15 min after the previous dose of fentanyl, altered as follows: a 10% increase in heart rate, a 10% increase in arterial pressure, a 15% increase in airway pressure, or the appearance of lachrymation or sweating.

Blood samples were obtained before the induction of anaesthesia, at the beginning and the end of surgery, and on the first postoperative day to measure the plasma concentrations of the endogenous opioid β-endorphin. β-Endorphin concentration was measured by radioiummunoassay, as previously described, after separation by high pressure liquid chromatography (Panerai et al., 1983).

All patients were informed about the design of the study and gave their consent to the administration of baclofen and the blood sampling.

Statistical analysis of results was obtained by analysis of variance followed by Duncan test for multiple comparisons.

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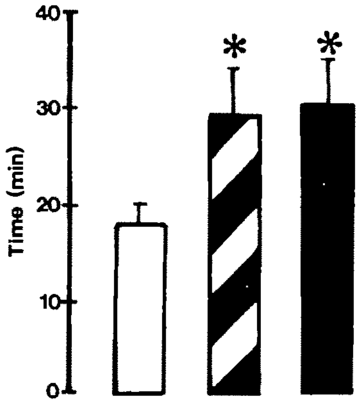

FIG. 1. Effect of pretreatment with saline (open column), baclofen i.m. (cross-hatched column) or baclofen i.v. (black column) on the time between the administrations of fentanyl. $^{*}P < 0.01$ *v.* saline.

TABLE I. *β-Endorphin plasma concentrations (mean ± SEM)*

Time	Concentration (fmol ml^{-1})
Before surgery	30 ± 12
During surgery	50 ± 15
After surgery	36 ± 10
24 h after surgery	34 ± 12

RESULTS

Figure 1 shows the intervals of time between the individual doses of fentanyl. It shows that baclofen, administered either i.m. for 5 days, or i.v. immediately before the beginning of surgery, induced a significant increase in the mean time between the increments of fentanyl.

The data obtained also indicate that those patients receiving baclofen required less fentanyl. The amounts of fentanyl administered during the surgical procedure were significantly less ($P < 0.001$) in groups 2 (0.0070 mg kg^{-1}) and 3 (0.0063 mg kg^{-1}) than that required by the patients pretreated with saline (0.0101 mg kg^{-1}).

Table I shows that the β-endorphin plasma concentrations did not change significantly before, during or after surgery, and that they were similar in the three groups.

DISCUSSION

Our data are consistent with the data obtained in the experimental animal, suggesting that baclofen can potentiate opioid-induced analgesia.

At present we do not have a clear explanation for these results, although a few hypotheses can be put forward. We can exclude, in all probability, the involvement of β-endorphin in this effect of baclofen, although other endogenous opioids might be involved.

Baclofen can be thought of as acting through two different mechanisms. The most obvious action is through a GABAergic mechanism, since it has been shown that it can bind to GABA-B receptors (Bowery, 1982) and act as GABA agonist. Consistent with this observation, several GABA-ergic compounds have been shown to potentiate opioid-induced analgesia when administered peripherally (De Feudis, 1982). Moreover, GABA itself and other GABAergic compounds have been shown to elicit analgesia which is not reversible by naloxone (De Feudis, 1982). This observation is also consistent with our data, that seem to exclude a role for endogenous opioids in our particular study. Baclofen can also directly inhibit the effects of substance P-mediated neurotransmission (Saito, Konishi and Otsuka, 1975) and, therefore, inhibit the primary afferent neurones at the spinal level (Capek and Esplin, 1982).

Our results, although preliminary and obtained under specific conditions, offer interesting suggestions for the clinical use of the combination of baclofen and an opioid which will decrease the amounts of opioid required in anaesthesia and, possibly, in the treatment of chronic pain — if our results can be confirmed in an appropriate model.

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EVALUATION OF THE COMBINED EFFECTS OF ATROPINE AND NEOSTIGMINE ON THE LOWER OESOPHAGEAL SPHINCTER

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SUMMARY

The effects, on the lower oesophageal sphincter, of the simultaneous administration of atropine and neostigmine were studied in 10 healthy patients undergoing gynaecological surgery. Atropine 1.2 mg and neostigmine 2.5 mg were given to antagonize neuromuscular blockade at the termination of surgery. For the succeeding 15–20 min, frequent measurements of lower oesophageal sphincter pressure (LOSP) were made whilst anaesthesia was maintained. It was demonstrated that this drug combination resulted in a significant decrease in LOSP initially, but that this potentially deleterious effect was transient in nature.

The lower oesophageal sphincter (LOS) is a physiological sphincter, situated at the lower end of the oesophagus, which can be identified and investigated by means of intra-luminal oesophageal manometry (Dodds and Hogan, 1980). There is now general agreement that the intrinsic tone of the LOS represents the major barrier to gastro-oesophageal reflux (Cohen and Harris, 1972; Fisher et al., 1977) and, as its functional integrity is affected by drugs used in anaesthetic practice, this zone of increased intraluminal pressure is of considerable clinical relevance to anaesthetists. As the tendency to gastro-oesophageal reflux is related to the intrinsic tone of the LOS, it follows that any drug which decreases LOS tone may be expected to increase the possibility of regurgitation, whereas drugs that increase LOS tone may well reduce this risk. This concept may be expressed in quantitative terms by calculation of the so-called Barrier Pressure (BrP), that is, the pressure differential between the LOS and the stomach (BrP = lower oesophageal sphincter pressure (LOSP) minus gastric pressure (GP)). Thus, the BrP is a measure of the overall resistance preventing gastro-oesophageal reflux.

Numerous investigators have demonstrated clearly that atropine causes a consistent decrease in LOSP and BrP when given i.v., an effect that is measurable within 1–3 min and persists for at least 60 min. This evidence has led to the recommendation that atropine be avoided during "rapid sequence induction". The effects of the combined administration of atropine and neostigmine on the LOS and BrP, when given to antagonize neuromuscular blockade during general anaesthesia, could also be important clinically, since at this time — as at the induction of anaesthesia — the airway may be transiently unprotected whilst reflexes are obtunded.

The purpose of the present study was to examine in detail the combined actions of atropine and neostigmine on lower oesophageal events when both drugs were given simultaneously, in standard clinical doses, to antagonize neuromuscular blockade at the termination of general anaesthesia. In particular, emphasis was placed on following the time course of events in the lower oesophagus after the administration of this particular combination of drugs.

PATIENTS AND METHODS

Ten healthy female patients undergoing elective intra-abdominal gynaecological surgery gave informed consent to participate in the study, which was approved by the Institutional Ethical Committee. All patients were free from coincidental gastrointestinal, respiratory or cardiovascular

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disease and, where appropriate, had refrained from smoking for the 8 h before surgery.

Each patient received a standardized anaesthetic technique. Pre-medication consisted of diazepam 0.2 mg kg^{-1} orally 2 h before the induction of anaesthesia. Thiopentone sodium 4 mg kg^{-1} was used to induce anaesthesia and tracheal intubation was facilitated by the administration of pancuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide and 0–1% enflurane in oxygen. Morphine sulphate was given for analgesia as thought necessary and artificial ventilation was adjusted as required to maintain normocapnia.

The oesophageal manometry tube consisted of a silastic orogastric tube (3 mm in diameter) into which were embedded three subminiature strain-gauge pressure transducers at distances of 5, 10 and 15 cm from the distal tip (Gaeltec Ltd, Isle of Skye, Scotland). This manometry tube was connected via a pre-amplifier to a multi-channel chart recorder (Linear Recorder Mk 111). The performance of this pressure recording system was assessed at frequent intervals during use. Calibration, or zero baseline drift, is insignificant over periods of time in excess of 90 min or with variations in ambient temperature of 1–2 °C. Before each investigation the whole system was calibrated in a water column (scale 0–50 cm H_2O) at 37 °C and this manoeuvre was repeated at the end of each study to confirm the absence of significant calibration or zero baseline drift. When a stable anaesthetic state had been achieved, the oesophageal manometry tube was passed through the patient's mouth until all three pressure transducers were in the stomach. Once a stable recording of gastric pressure had been obtained from each transducer, the oesophageal manometry tube was withdrawn slowly, allowing each pressure transducer to pass from the stomach through the LOS into the oesophagus. In this way, three sequential recordings of GP, LOSP, and oesophageal pressure (OP) were obtained. This "pull-through" manoeuvre was continued until an OP trace was seen on the distal transducer, the whole process taking from 20 to 40 s. The proximal transducer allows discrimination between pressure changes induced by swallowing and peristalsis and those attributable to the LOS. All measurements were related to the end-expiratory point and if at any time coughing or straining interfered with recording, that particular measurement was discarded. A more detailed description of this methodology, together with illustrations that demonstrate the effect of swallowing and peristalsis on lower oesophageal pressure tracings appears in our two previous publications (Smith, Dalling and Williams, 1978; Cotton and Smith, 1984). On completion of surgery, and having obtained three control measurements of GP, LOSP and OP, each patient was given atropine 1.2 mg and neostigmine 2.5 mg as a bolus i.v. After this, a "pull-through" manoeuvre yielding three measurements of GP, LOSP and OP was performed at 1-min intervals for 20 min. During and after the antagonism of neuromuscular blockade, anaesthesia was maintained with 70% nitrous oxide and 0–2% enflurane in oxygen. This prevented the patient from straining and coughing, either of which makes the lower oesophageal pressure tracing difficult to interpret and causes inaccuracies in quantitating the actual measurements of pressure. "Pull-through" manoeuvres were performed as frequently as the pressure recording system would allow, to minimize the chance of missing any transient effect of the drug combination.

All results were assessed statistically using analysis of variance followed by Student's t test for unpaired data.

RESULTS

The simultaneous administration of atropine 1.2 mg and neostigmine 2.5 mg decreased BrP from 26.9 ± 3.6 cm H_2O (±SEM) to 18.1 ± 2.56 cm H_2O (±SEM) at 1 min after administration ($P < 0.05$) (fig. 1). At 2 min after administration, BrP decreased further to 17.4 ± 2.89 cm H_2O (±SEM) — a value still significantly lower than

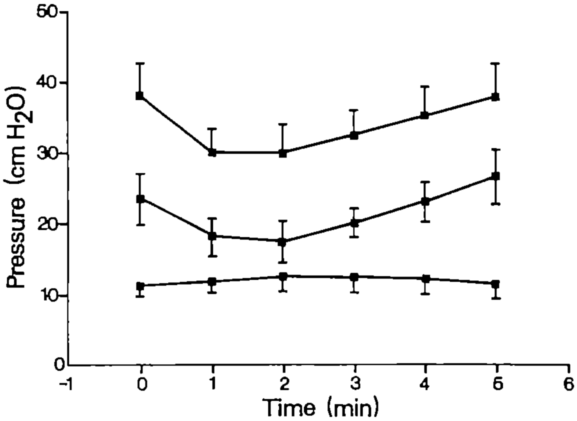

FIG. 1. Effect of the simultaneous administration of atropine 1.2 mg and neostigmine 2.5 mg on LOSP (upper profile), BrP (middle profile) and GP (lower profile). Mean ± SEM, $n = 10$.

the value before antagonism ($P < 0.05$). By the time 3 min had elapsed after the administration of the atropine and neostigmine, BrP had increased to 20.1 ± 2.07 cm H_2O, which was not significantly different from the control values. Further measurements performed at 1-min intervals for 15 min (three patients) or 20 min (seven patients) after the drug administration revealed values for BrP not significantly different from control.

DISCUSSION

The effect on the LOS of an individual drug, or of a combination of drugs, is difficult to evaluate during the course of general anaesthesia when many other drugs are given and many physiological changes occur. For instance, certain drugs (e.g. atropine) when given alone may have a specific effect on the LOS, the magnitude of which may be quantified and the time course described by oesophageal manometry techiques. However, when two or more drugs are given in combination the effect of one may predominate and many factors determine the overall effect on BrP, the magnitude of which may vary with time, as a result of pharmacokinetic and other differences between the drugs. It should also be emphasized that there is a wide variation in basal LOSP (Dent et al., 1980) and, even in the same individual, LOSP (which is a dynamic, continuous variable) may change considerably over quite short periods of time (Dodds et al., 1980). For this reason, multiple and frequent measurements should be obtained if important drug effects are not to be confused with the normal variability in basal LOSP or be missed altogether. The frequency at which measurements can be made depends upon the actual technique of oesophageal manometry as well as the design of the study. Using the present measuring system it is possible to perform "pull-through" manoeuvres every minute in the anaesthetized subject and we believe that this is sufficient to obtain a reliable record of lower oesophageal events.

In contrast to the previously cited work on the effect of atropine on LOSP and BrP (Brock-Utne et al., 1977; Cotton and Smith, 1981), less information is available on the effects of neostigmine on the LOS in human subjects. It has been shown that cholinergic stimulation with either cholinomimetic drugs such as bethanocol (Roling, Farrell and Castell, 1972) or the anticholinesterase edrophonium (Christensen and Daniel, 1968) increases LOSP and one would expect neostigmine to have similar effects.

Atropine in combination with neostigmine is used routinely to antagonize the effects of non-depolarizing myoneural blocking agents at the motor end-plate and it is not surprising to discover that LOSP and BrP are influenced by this combination of drugs. Kim, Patdu and Kim (1977) demonstrated an increase in LOSP after the administration of atropine 0.017 mg kg^{-1} and neostigmine 0.05 mg kg^{-1} to antagonize the effects of dimethyltubocurarine.

In that study the exact timing of this increase in LOSP relative to the administration of the "reversal" drugs was not recorded and the manometric methodology using balloons as pressure sensors is thought to be inaccurate (Rinaldo and Levey, 1968). In contrast, Brock-Utne and colleagues (1978), in a study on pregnant women undergoing elective Caesarean section, found that atropine 1.2 mg and neostigmine 2.5 mg resulted in a slight decrease (albeit insignificant) in LOSP. In addition, these authors noted, in the same group of patients, that doubling the dose of neostigmine significantly increased LOSP and BrP 1 min after the administration of the antagonizing drugs. This study was complicated by the use of both metoclopramide and atropine before the induction of anaesthesia and may also be criticized on the grounds that only a single measurement was performed before and after the administration of the drug combination. Both these drugs have significant effects on LOSP and BrP which persist for some time. In addition, in a study designed to investigate gastro-oesophageal reflux in late pregnancy Hey and co-workers (1977) demonstrated that pregnant women, with or without symptoms of heartburn, had lower mean BrP than the control group. This suggests that the drug effects noted in parturients may well not pertain to the population in general.

In the present study, multiple measurements of LOSP, GP and OP were made at 1-min intervals after the administration of atropine 1.2 mg and neostigmine 2.5 mg. It was found that LOSP and BrP decreased initially to values significantly lower than those recorded before the administration of the drugs (fig. 1). After 3 min had elapsed, both LOSP and BrP had increased to values not significantly different from control—an increase in LOSP that was sustained for 15–20 min. It is apparent, therefore, that when atropine and neostigmine are given simultaneously, at first the potentially deleterious effect of atropine predominates, but this is rapidly negated by the action of neostigmine such that by 3 min the net effect on LOSP and BrP is negligible.

Despite advances in modern anaesthesia, regurgitation followed by pulmonary aspiration and its sequelae remains an important cause of morbidity and mortality. A recent investigation into anaesthetic morbidity and mortality in Great Britain (Lunn and Mushin, 1982) revealed that, of the total of 58 deaths described as completely attributable to anaesthesia, 11 probably resulted from the aspiration of gastric contents. In an effort to reduce the risk of aspiration, a variety of physical and pharmacological manoeuvres has been recommended, including the use of drugs which increase BrP (domperidone and metoclopramide) and the avoidance of drugs which decrease BrP (atropine, hyoscine, glycopyrrolate) in situations when regurgitation is likely.

The results of this study suggest that, in the clinical situation, when atropine or neostigmine are given simultaneously in the usual doses, the effects of neostigmine negate to a large extent the potentially hazardous effect of atropine on the LOS, provided that at least 3 min has elapsed since administration. After this time the patient should not be at increased risk of regurgitation from decreases in BrP.

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A DOUBLE-BLIND STUDY OF MOTOR BLOCKADE IN THE LOWER LIMBS

Studies During Spinal Anaesthesia with Hyperbaric and Glucose-free 0.5% Bupivacaine

K. H. AXELSSON, G. B. WIDMAN, A. E. A. SUNDBERG
AND S. HALLGREN

SUMMARY

Sensory and motor blockade were studied double-blind during spinal anaesthesia in 20 urology patients who received 0.5% bupivacaine solution 4 ml with or without glucose. Using a new method for determining muscle strength, motor blockade during anaesthesia was recorded quantitatively for flexion of the hip, extension of the knee and plantar flexion of the big toe. Movements of the lower part of the thoracic cage were recorded at the same time. Complete motor blockade of longer duration was observed for all three movements following the administration of the glucose-free solution compared with the solution containing glucose. During the regression phase, the muscle strength returned significantly later (knee extension and hip flexion) when glucose-free bupivacaine solution was given. There was no significant difference between the two anaesthetic solutions regarding plantar flexion of the big toe during this phase. For hip flexion (L1–L3) there was no noteworthy difference between the levels of analgesia and the motor blockade, whereas for plantar flexion of the big toe (L5–S2) the level of analgesia was 2–3 segments higher than the level of motor blockade. Thoracic movements (maximal inspiration to normal expiration) did not appear to be notably influenced by the level of analgesia. Complete regression of motor blockade was not observed for any of the movements at grade 0 of a modified Bromage scale. Not until 1.5–2 h after the attainment of this grade was the muscle strength of all movements restored (90% of control value).

Lower abdominal surgery, vascular surgery and orthopaedic procedures on the lower limbs require good motor blockade. With certain local anaesthetics, however, the correlation between the intensity of motor blockade and the quality of sensory blockade seems to be unsatisfactory. During extradural anaesthesia 0.5% amethocaine and 1% etidocaine produce more profound motor paralysis than 0.5% bupivacaine (Bromage, 1969; Bromage, Datta and Danford, 1974; Engberg, Holmdahl and Edström, 1974). Glucose-free 0.5% bupivacaine provides a longer duration of motor blockade than 0.5% bupivacaine containing glucose following subarachnoid administration (Bengtsson, Edström and Löfström, 1983; Krüger et al., 1983; Axelsson, Edström and Widman, 1984). In these investigations the motor blockade in the lower extremities was estimated according to the scale proposed by Bromage (1965).

A new method of quantitating muscle strength (Axelsson et al., 1984) can be used to measure the isometric muscle strength in the lower extremities in non-anaesthetized patients, and in patients undergoing spinal anaesthesia.

The aims of this investigation were: (1) to test this method clinically, and to compare the degrees of sensory and motor blockade provided by the subarachnoid injection of 0.5% bupivacaine 4 ml with and without glucose; and (2) to compare the objectively recorded changes in muscle strength with the results using a modified Bromage scale, and with sensory blockade as assessed by pin-prick.

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PATIENTS AND METHODS

Measurement of motor and sensory blockade

The patients were studied before and after operation with the aid of an apparatus for determining muscle strength (Axelsson et al., 1985). The maximal isometric strength that was generated by the different movements of the lower limbs (see below) was transmitted to a force transducer (Alpha load beam 500 N BLH Electronics). The signals from the transducers were amplified and recorded on a four-channel Siemens–Elema Minograf 34. The error of the method was small (Axelsson et al., 1985).

To obtain supplementary information, mercury strain gauges (Medimatic) were used to measure the movements of the lower part of the thorax during respiratory movements which corresponded to the inspiratory capacity (tidal volume + inspiratory reserve volume). For technical reasons, respiratory movements could be recorded in only nine patients in the group that received glucose-free bupivacaine solution and in eight patients in the glucose-containing bupivacaine group.

The patient lay in the lithotomy position with his hands on his abdomen. The muscle strength in both legs was recorded simultaneously. The following movements were performed (fig. 1):

(1) Flexion of the hip joint (femoral nerve L1–L3): The muscle force was taken up by a leather-covered plate and transferred via a lever to a freely movable metal rod; this in turn transmitted it to a force transducer.

(2) Extension of the knee joint (femoral nerve L2–L4): the muscle force was transmitted to a transducer via a leather strap fixed around the ankle.

(3) Plantar flexion of the big toe (tibial nerve

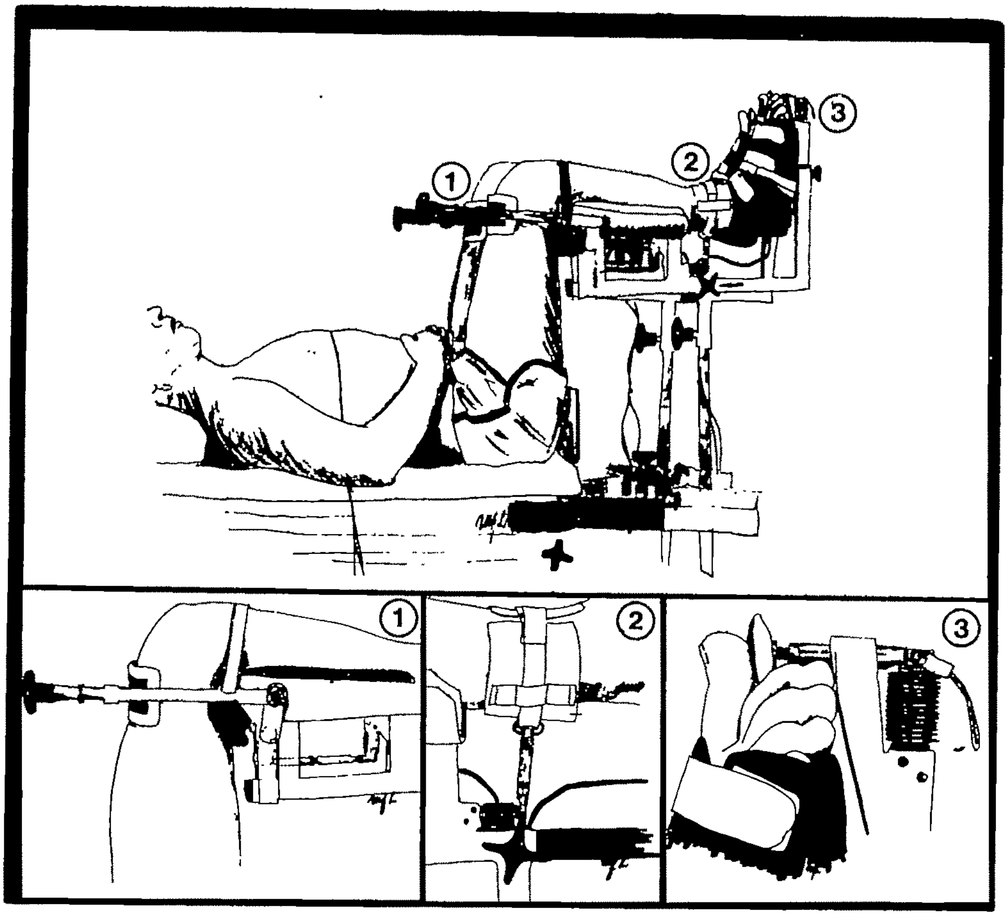

FIG. 1. Diagram of the apparatus for measuring muscle strength.

L5–S1, S2): this movement was performed against a rigid silicon plate which was connected to the force transducer.

A *set of tests* consisted of these three movements performed five times. The mean value of the measurements for each movement was calculated on both left and right sides. The set of tests included also five measurements of thoracic movement, and their mean value was calculated in a similar manner.

During the onset and regression of the spinal anaesthetic, the mean value of the isometric strength of each movement in every set of tests was calculated and was expressed as the percent deviation from the control value (mean value of four sets of tests before spinal anaesthesia). The quantitatively determined degree of motor blockade during spinal anaesthesia was presented graphically for each patient. In order to compare motor blockade in the two groups of patients who received 0.5 % bupivacaine 4 ml with and without glucose, respectively, a calculation was made for each movement in every patient of the time taken for 75, 50, 25 and 0 % of the control value during onset, and for 0, 25, 50, 75 and 90 % of the control value to be regained during the regression of blockade. The mean values of these times for the different levels were calculated for the two bupivacaine solutions, and are presented graphically (figs 3 and 4). The muscle strength of the lower extremities was considered to be restored completely when the strength of each movement had returned to 90 % of its control value, and the patients were able to walk about 5 m.

Simultaneously with the tests of muscle strength (during onset of blockade), the degree of motor blockade was recorded in terms of a four-grade modified Bromage scale (0–3): 0 = no paralysis; 1 = inability to raise extended leg (just able to move knees); 2 = inability to flex knee (able to move feet only); and 3 = inability to flex ankle joint and first digit.

During the regression phase, grades 2 and 1 were given a modified definition, while grades 0 and 3 were unchanged: 3 = inability to flex ankle joint and first toe; 2 = just able to move knee; 1 = ability to raise extended leg but inability to flex ankle joint and first digit; and 0 = no paralysis.

During the onset of sensory blockade the level of analgesia was determined by pin prick until maximum cephalad spread of the analgesia had been attained. During regression, corresponding recordings were made every 15–30 min or, in certain patients, at every muscle strength test, until normal sensation had returned.

TABLE I. *Patient characteristics (mean ± SEM)*

	Age (yr)	Weight (kg)	Height (cm)
Glucose-free bupivacaine 20 mg	67.2 ± 1.92	82.5 ± 2.86	177.8 ± 1.47
Bupivacaine 20 mg + glucose 80 mg ml^{-1}	63.9 ± 1.91	78.4 ± 2.43	177.7 ± 2.56

Patients

The double-blind study comprised 20 patients (ASA 2–3) undergoing urological surgery (TUR of cancer of the urinary bladder). They had neither spinal deformity, nor mental or neurological disorder. The patients were comparable in age, height and weight (table I). They were given verbal and written information about the study, which was approved by the Ethics Committee of the Örebro Medical Centre Hospital.

Procedure

The patients were allocated randomly to two groups of 10 patients each. One group received 0.5 % bupivacaine solution 4 ml in 0.9 % sodium chloride (density 1.000 at 37 °C, pH 6.2); the other group received 0.5 % bupivacaine 4 ml containing 8 % glucose monohydrate (density 1.021 at 37 °C, pH 5.0–6.0). No premedication was given, apart from atropine 0.5 mg i.v. just before the intrathecal injection.

With the patient in the sitting position, lumbar puncture (L3–L4) was performed (22-gauge needle) and the appropriate solution administered (0.5 ml s^{-1}). The patient remained sitting for 2 min, after which he was placed in the lithotomy position. All patients received 500 ml of Ringer's glucose solution just before the lumbar puncture. Any decrease in systolic arterial pressure by more than 30 % was treated initially with etilefrine chloride (Etilefrinum) or dihydroergotamine (Orstanorm).

As soon as the patient had been placed in the lithotomy position, measurements of muscle power were undertaken: first, plantar flexion of the big toe, then extension of the knee and, finally, flexion of the hip. The measurements were repeated until motor blockade was complete or a steady state had been reached. Thoracic movements were recorded with the strain gauge during the onset of blockade once the level of analgesia had stabilized. Determinations of muscle strength were performed repeatedly during the regression of blockade.

One to two days after the operation the patients were questioned about possible post-spinal complications. In addition, they were asked to communicate with the authors should any complication arise following discharge from hospital.

Definitions

Regression time. The time from commencement of regression of blockade until 90% of the initial muscle strength had been regained for each movement.

Total regression time. The time from the commencement of regression of blockade until 90% of the initial muscle strength had been regained for all movements.

Statistics

Student's t test for independent samples was used. The level of significance was $P < 0.05$.

RESULTS

Sensory blockade

There was a rapid onset of analgesia in both groups. Fifteen minutes after the intrathecal injection, the upper level of analgesia was T7–T8 and after 30 min it had reached T6–T8 irrespective of whether the bupivacaine was with or without glucose. There were no significant differences in the spread of the analgesia between the patients who had received the two different solutions (fig. 2). All patients in both groups had thoracic analgesia.

The duration of analgesia was significantly longer in the lower thoraco–lumbar segment when bupivacaine without glucose had been given. With the glucose-free solution the analgesia at the level of T11–T12 lasted for 210 min, compared with 150 min for the solution containing glucose. The corresponding durations for the L3–L4 level were 270 and 210 min, respectively.

Onset of motor blockade

As there was no significant difference in the degree of motor blockade between the left and right sides, descriptions of motor block have been based on the mean result from the two sides. All patients in the glucose-free group had complete motor paralysis. In the glucose-containing group one patient had complete motor blockade in the muscles performing plantar flexion of the big toe, while knee extension and hip flexion remained at muscle strength values of 19 and 10% of the control values 30 min after spinal injection. For

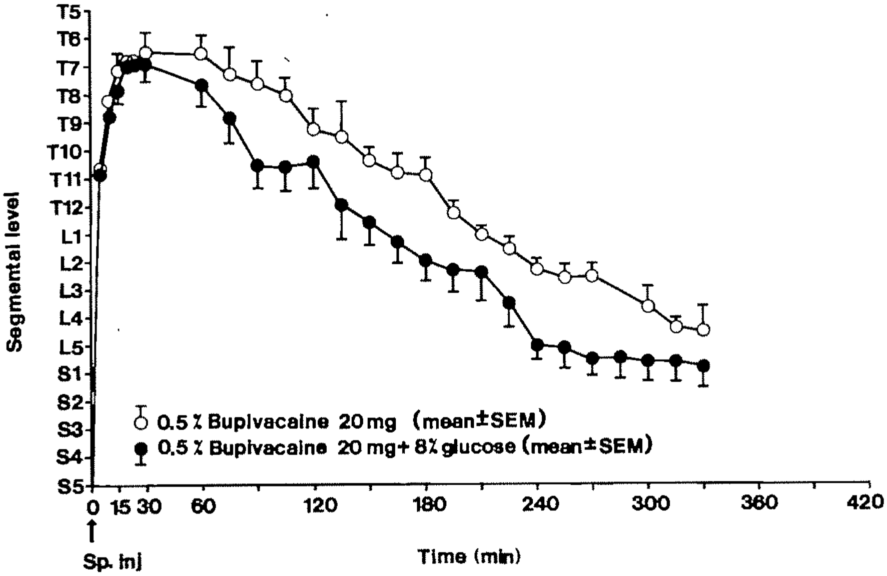

FIG. 2. Sensory blockade in spinal anaesthesia: segmental spread of analgesia (mean ± SEM).

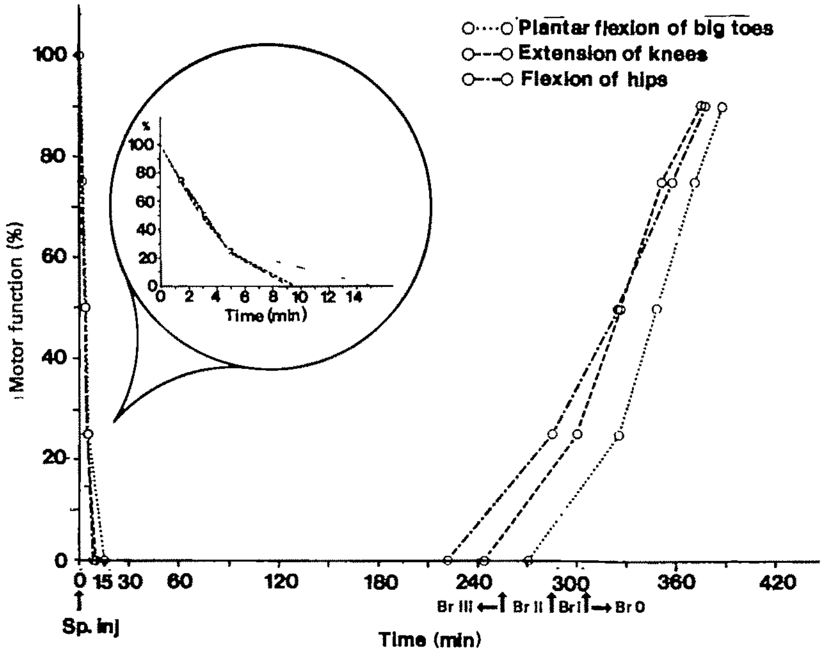

FIG. 3. Onset (left and the circle) and regression (to the right) of motor blockade following spinal injection of 0.5% glucose-free bupivacaine 4 ml. The arrows indicate the times at which different grades on the Bromage scale were reached. There was no significant difference between the three types of movement. At Bromage 0 there was a considerable degree of motor blockade.

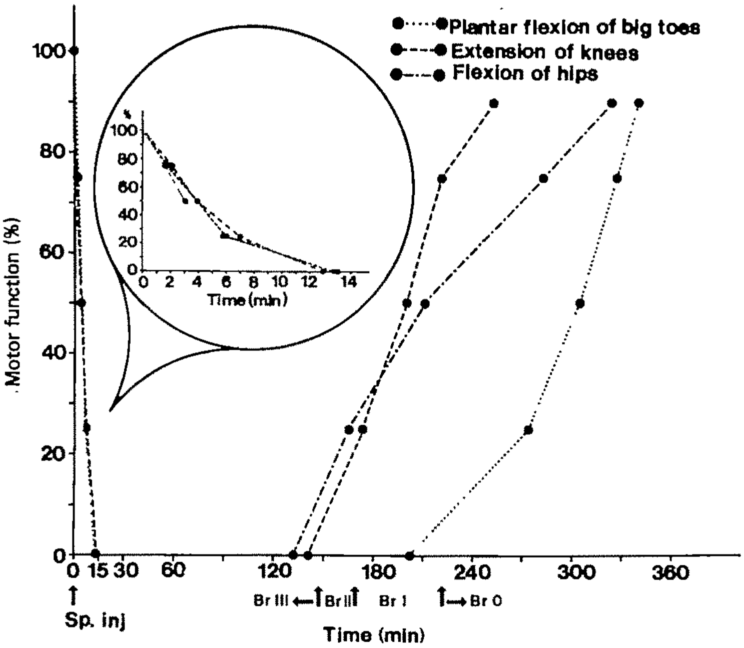

FIG. 4. Onset (left and the circle) and regression (to the right) of motor block following spinal injection of 0.5% bupivacaine 4 ml with 8% glucose. The time of onset and regression at 0% level is based on nine patients (knee extension and hip flexion). The arrows indicate the Bromage grading. At Bromage 0 the strength of knee extension had largely returned, while the motor block still remained in the other movements.

this reason, the time of onset and regression at 0% level is based on nine patients.

The onset of motor blockade was rapid in both groups (figs 3 and 4). Only 50% of the initial muscle strength of the three muscle movements remained 3–4 min after injection. After 5 min in the glucose-free group and 5–8 min in the glucose group, the muscle strength was 25% of its control value. Fifteen minutes after injection, complete motor blockade was attained with both solutions. During the onset of motor blockade there were no significant differences between the two groups.

Regression of motor block

The patients receiving 0.5% bupivacaine without the addition of glucose could begin to flex their hips 225 min after the injection, and knee extension and plantar flexion of the big toe began to return about 20 and 25 min later, respectively (fig. 3). During regression there was no significant difference between the restoration of muscle strength in the three types of movement. Regression time was 120–150 min for each movement (fig. 3), and total regression time was almost 160 min. Ninety per cent of the muscle strength had returned for plantar flexion of the big toe and extension of the knee, after 390 and 375 min, respectively.

In the patients receiving 0.5% bupivacaine with the addition of glucose, ability to flex the hips began to return 130 min after the spinal injection, and about 10 min later knee extension became possible (fig. 4). Plantar flexion of the big toe recovered about 60 min after hip flexion. The muscle strength of plantar flexion of the toe took significantly longer to return to the levels of 0, 25 and 50% of the initial value than that of the other two movements. At the 75% and 90% levels there were significant differences in the duration between extension of the knee and plantar flexion of the big toe. The regression time for the different types of movement varied between 120 and 180 min. The total regression time was just over 200 min. The muscle strength of plantar flexion of the big toe and of extension of the knee returned 340 and 255 min, respectively, after the spinal injection (fig. 4).

On comparing the glucose and glucose-free groups, the duration of complete motor blockade was found to be significantly longer for all movements in the latter group.

During the regression phase, on the average, hip

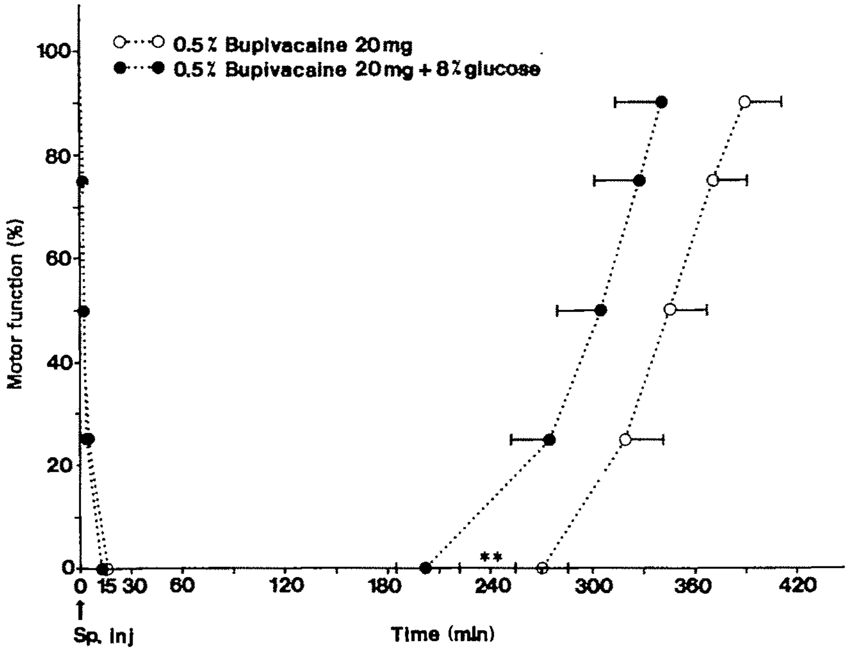

FIG. 5. Motor blockade in spinal anaesthesia. Comparison of 0.5% bupivacaine 4 ml with and without added glucose. Plantar flexion of big toe: The glucose-free solution gave significantly longer complete motor block (0% level) than the solution containing glucose.

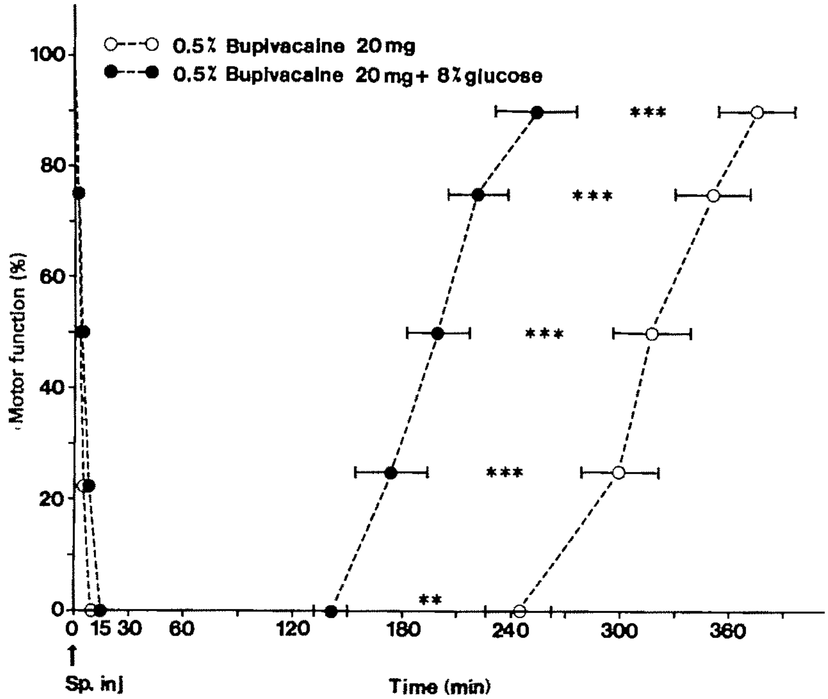

FIG. 6. Motor blockade in spinal anaesthesia. Comparison of 0.5% bupivacaine 4 ml with and without added glucose. Extension of the knee: The time of onset and regression at 0% level is based on nine patients (0.5% bupivacaine 4 ml with glucose). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

flexion could be performed earlier than knee extension and plantar flexion of the big toe, irrespective of local anaesthetic. This order of sequence was noted in seven of 10 patients in the glucose-free group and in three of 10 in the glucose group. Hip flexion and knee extension returned simultaneously in one of 10, and in six of 10 patients in these two groups, respectively. Plantar flexion of the toe returned last in eight of 10 in the glucose-free group and in all patients of the glucose group. Regression of motor blockade commenced significantly later for plantar flexion of the toe when glucose-free solutions had been given, compared with the solution containing glucose. The lengths of time required to reach the levels of 25, 50, 75 and 90% of the control value did not differ significantly between the two groups (fig. 5). For extension of the knee (fig. 6) and flexion of the hip (fig. 7), except for hip flexion at the 90% level, the isometric strength was restored significantly more slowly in the glucose-free group than in the group that received the glucose-containing solution.

Comparison between modified Bromage scale and method for measuring muscle strength

Using the modified Bromage scale, the duration of motor blockade was found to be significantly longer in those patients receiving glucose-free solution than in the group that received the glucose-containing solution (table II).

In the glucose-free group, of the initial strength of knee extension and hip flexion, 5% and 16% respectively, had returned when the modified Bromage grade changed from 3 to 2 (fig. 3). At a modified Bromage grade of 0, the muscle strength of plantar flexion of the big toe, knee extension and

TABLE II. *Duration of motor bock (min) as recorded by the Bromage scale. A significant difference between the two anaesthetic solutions is indicated by the* t *value.* $^{**}P < 0.01$; $^{***}P < 0.001$

Bromage grade	Glucose-free bupivacaine 20 mg	Bupivacaine 20 mg + glucose 80 mg ml^{-1}	*t*
3	257±20.3	148±18.3	4.09***
2	285±20.3	170±16.9	4.36***
1	307±21.3	222±14.6	3.32**

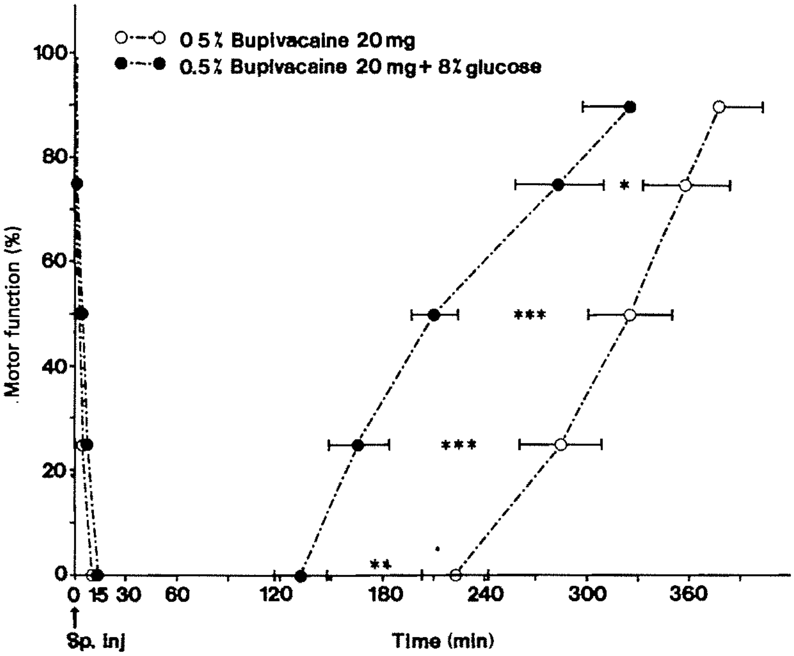

FIG. 7. Motor blockade in spinal anaesthesia. Comparison of 0.5% bupivacaine 4 ml with and without added glucose. Flexion of the hip: The time of onset and regression at 0% level is based on nine patients (0.5% bupivacaine 4 ml with glucose). $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

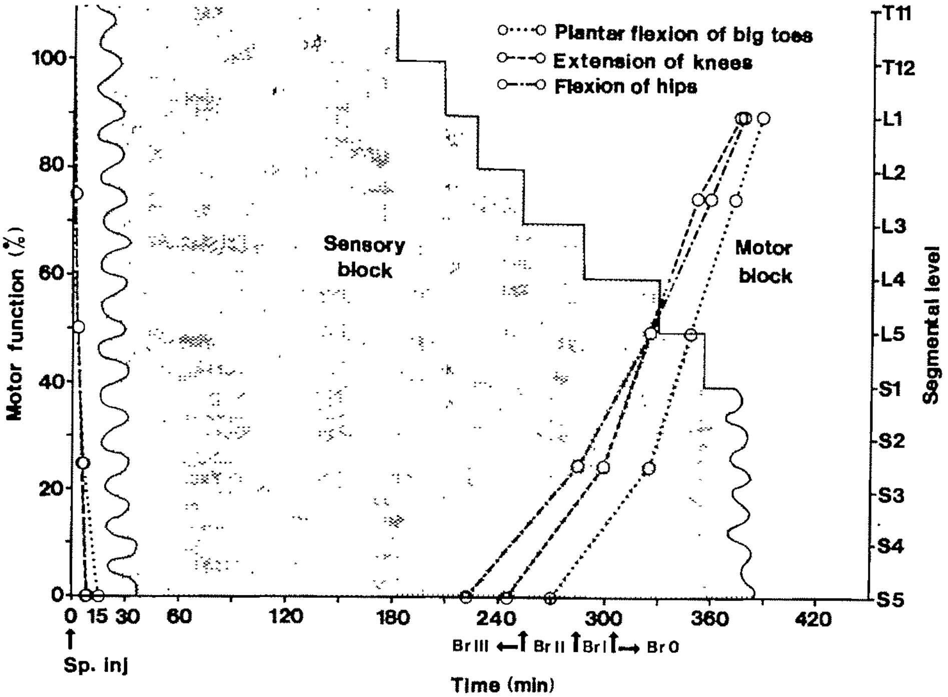

FIG. 8. Sensory and motor blockade in spinal anaesthesia. The level of analgesia correlated with motor blockade curve after spinal injection of 0.5% glucose-free bupivacaine 4 ml. The isometric strength of hip flexion returned at the same time as the analgesia (pin-prick) changed from L1 to L2. When the level of analgesia changed from L5 to S1, the strength of knee extension had largely returned, while the strength of plantar flexion of the big toe was still reduced.

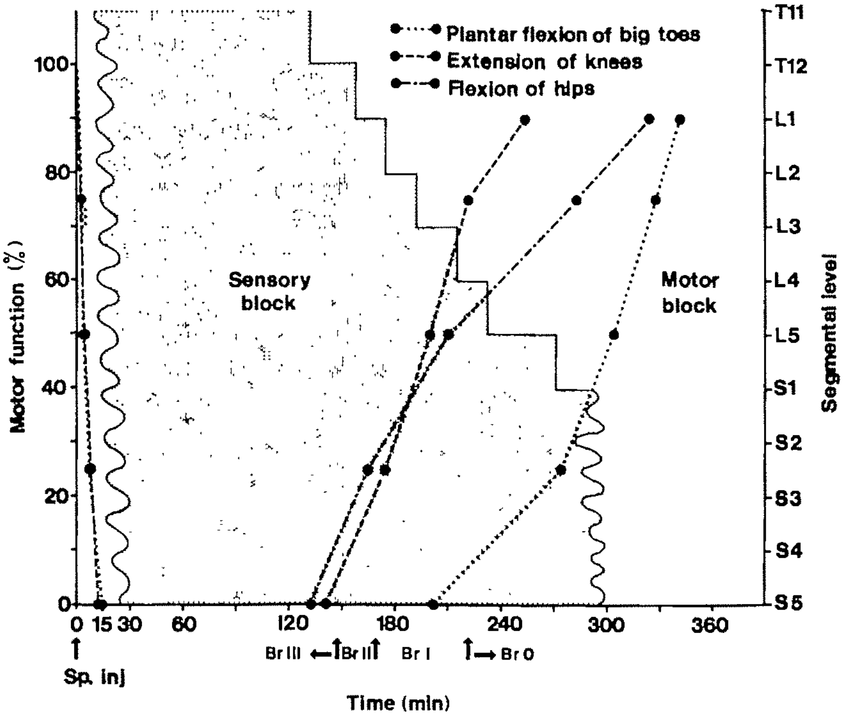

FIG. 9. Sensory and motor blockade in spinal anaesthesia. The level of analgesia correlated with motor blockade curve after spinal injection of 0.5% bupivacaine 4 ml with 8% glucose. The time of onset and regression at 0% level is based on nine patients (knee extension and hip flexion). The isometric strength of hip flexion and knee extension began to return when the upper level of analgesia was at T12. At the S1 level a considerable degree of motor block remained for plantar flexion of the big toe.

hip flexion had regained 16%, 32% and 38% of their control values, respectively (fig. 3). In the glucose group, grade 3 on the modified Bromage scale changed to grade 2 when 5% and 13% of the initial muscle strength had returned for knee extension and hip flexion, respectively. Modified Bromage grade 1 changed to 0 when the corresponding figures for plantar flexion of the big toe, knee extension and hip flexion were 8%, 75% and 58%, respectively (fig. 4).

Relation between segmental level of analgesia and motor blockade

The strength of hip flexion and knee extension (L1–L4) began to return when the level of analgesia (to pin-prick) was around L1–L2 in the glucose-free group (fig. 8) and at T12 in the group that received the glucose-containing solution (fig. 9). For plantar flexion of the big toe (L5–S2), the muscle strength returned when the level of analgesia was around L3–L4 for both solutions. When grade 3 on the modified Bromage scale changed to grade 2, the upper level of analgesia lay at around L3 in the glucose-free group and at T12 in the glucose-containing group. At modified Bromage grade 0 the upper level of analgesia lay at around L4 for both solutions (figs 8, 9).

Patients were mobilized once they had regained 90% of the initial muscle strength at each movement bilaterally, and after the heart rate had been assessed in the sitting position. This occurred after about 420 min in the glucose-free group and after 395 min in the other group. This difference was not significant.

Thoracic movements did not appear to be influenced by the extent of the spinal anaesthesia. Even when the upper level of analgesia lay at about T3, the deflections showed a pattern similar to that obtained under control conditions.

Complications

A decrease in systolic arterial pressure of more than 30% was noted in two patients in the glucose-free group and in three in the glucose

TABLE III. *Frequency of reductions in systolic arterial pressure (percentage of control)*

Decrease in arterial pressure (%)	Bupivacaine 20 mg	
	Glucose-free	With glucose 80 mg ml^{-1}
20–30	2	2
$\geqslant 30$	2	3

group (table III). Two patients in each group were treated with etilefrine chloride and one patient was given dihydroergotamine. One patient in each group received additional atropine. In one of the five patients the duration of both sensory and motor blockade was longer than the average. One patient in the glucose-free group complained of nausea in connection with hypotension. No post-spinal headache occurred.

DISCUSSION

In most recent investigations of motor paralysis during spinal blockade, blockade has been assessed by the method proposed by Bromage (1965). However, the Bromage method is qualitative and does not permit of exact comparisons. Hitherto no method has been available for the quantitative determination of the degree of motor blockade. The apparatus used in this study was constructed to measure the maximal isometric strength in the lower extremities during spinal anaesthesia and so determine motor blockade quantitatively. At the same time, the thoracic respiratory movements could be recorded to assess the motor blockade of the lower intercostal muscles.

A comparison of the two groups of patients who had received 0.5% bupivacaine 4 ml, with or without the addition of glucose, found that complete motor blockade was of significantly longer duration (in all movements) when the glucose-free solution had been given. When all movements were included, in the glucose-free group the total regression time was significantly shorter than the duration of complete motor blockade. The opposite was found in the other groups. Thus, a glucose-free solution should be preferable for operations requiring prolonged complete motor blockade.

With regard to hip flexion and knee extension, the duration of motor blockade was significantly longer in the glucose-free than in the glucose-containing group. As the regression time for each movement was about 2–3 h irrespective of anaesthetic solution, the longer duration of motor blockade with the glucose-free solution must be attributable to a high concentration in the region L1–L4 which innervates the muscles for hip flexion and knee extension. The difference in the duration of motor blockade between the two anaesthetic solutions was greatest in the muscles performing knee extension. This indicates that the glucose-free solution was present at a higher concentration than the glucose-containing solution in the motor roots around the L2–L4 region, that is the site of the spinal injection.

The motor level during spinal anaesthesia is said to lie 2–3 segments below the sensory level (Freund et al., 1967). In the present study the sensory and motor levels differed by slightly less (by 0–2 segments) in the upper lumbar segments. In the sacral segments the difference was in accord with previously reported findings.

The use of the modified Bromage scale for recording motor blockade did not permit an equally reliable evaluation of the level of analgesia. When grade 3 on the modified Bromage scale changed to grade 2, there was some difference in the level of analgesia between the two solutions. At modified Bromage grade 0 the level of analgesia was the same for both solutions.

The original Bromage scale is based on the assumption that the onset of motor blockade takes place first in the hip and knee, followed by the foot and toe. According to our previous findings, motor blockade regresses last in the foot and toe and, consequently, we have altered the order of sequence of the scale so that it better fits with our clinical practice. In the present study, during regression, only seven of the 10 patients who received the glucose-free solution and three of the 10 in the glucose group matched the modified order of sequence (hip followed by knee and foot/toe last) when it was assessed by our method of measuring muscle strength.

Irrespective of which anaesthetic solution had been given, when motor blockade changed from grade 1 to 0, the muscle strength had not regained the normal value for any of the types of movement studied. In the group which received glucose in the solution, knee extension and hip flexion had returned to a greater extent (75% and 58%, respectively) than the corresponding movements in the glucose-free group (36% and 38%). Thus, modified Bromage grade 0 does not represent equal degrees of regression of motor blockade in patients receiving 0.5 % bupivacaine 4 ml with and without glucose. Not until 1.5–2 h had elapsed after Bromage grade 0 had been reached had the strength returned in all movements irrespective of anaesthetic solution.

Had the foot movement been tested alone (*cf.* Lanz et al., 1983), the difference in the duration of complete motor blockade between the two solutions would have persisted. No difference would have occurred during the regression, as was obtained in the present study when two other types of movements were investigated also. In seven of our patients motor blockade remained in one of the other two movements when the strength of plantar flexion of the big toe had returned to normal. Thus, to obtain more information on motor blockade associated with spinal anaesthesia, testing of three movements of the lower extremities is to be preferred to testing of the movement of the foot alone.

CONCLUSION

Glucose-free bupivacaine solution gave significantly longer complete motor blockade than bupivacaine solution without glucose. The muscle strength of hip flexion and knee extension returned significantly later after administration of the glucose-free anaesthetic solution. A shorter total regression time (all movements) in the glucose-free group than in the group that received glucose in the anaesthetic solution meant that the patients could be mobilized after almost the same length of time, 6.5–7 h, irrespective of which solution had been given — that is, not until 1.5–2 h had elapsed after Bromage grade 0.

ACKNOWLEDGEMENTS

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SPINAL ANAESTHESIA WITH 0.75% BUPIVACAINE AND 0.5% AMETHOCAINE IN 5% GLUCOSE

T. MARSTRAND, M. SØRENSEN AND S. ANDERSEN

SUMMARY

Three millititre of 0.75% plain bupivacaine and 0.5% amethocaine 3 ml in 5% glucose were used for spinal anaesthesia and compared in a double-blind study of 20 patients undergoing urological surgery. The onset time to maximum cephalad spread of sensory analgesia was approximately 45 min for bupivacaine and approximately 30 min in the amethocaine group (ns). The mean maximum spread of sensory analgesia was similar for both agents: T6–7 180 min after injection, although the cephalad spread of sensory analgesia with bupivacaine persisted for longer at a significantly higher level than that of amethocaine. Duration of sensory analgesia was significantly longer in the bupivacaine group from S3 to S5 and from T12 to L2 levels. Onset time to complete motor blockade of the lower limbs was similar for both agents. Nine of 10 bupivacaine patients and seven of the 10 patients receiving amethocaine had complete motor blockade of the lower limbs. Duration of motor blockade was significantly longer for all degrees in the bupivacaine group.

Amethocaine (usually with adrenaline) has been the standard agent for the provision of spinal anaesthesia in the United States and Europe although, during the past 6–7 yr, bupivacaine has been used for this purpose also (Nolte et al., 1977; Nightingale and Marstrand, 1981). However, there are only a few studies in which bupivacaine and amethocaine have been compared in a controlled fashion in a relatively homogeneous group of patients (Ekblom and Widman, 1966; Pflug, Aasheim and Beck, 1976; Lanz, Schellenberg and Theiss, 1979; Moore, 1980).

The present investigation compares a glucose-free solution of plain bupivacaine with the standard amethocaine solution (without vasopressor) in patients undergoing urological surgery. The solutions studied were 0.75% bupivacaine 3 ml and 0.5% amethocaine 3 ml in 5% glucose.

PATIENTS AND METHODS

Twenty patients (19 men) scheduled for urological surgery under spinal anaesthesia were included in the investigation (table I), which was approved by the Regional Ethical Committee. Informed consent was obtained. The patients were randomly distributed into two groups. Age, weight, and height were comparable between the groups (table II).

In most patients premedication consisted of diazepam 5–15 mg given by mouth 1–2 h before lumbar puncture. Before the lumbar puncture, an i.v. infusion of physiological saline was established, and the patient's cardiovascular system was

TABLE I. *Surgical diagnoses*

Surgical diagnoses	No. patients
Prostatic hypertrophy	11 (55%)
Bladder carcinoma or papilloma	7 (35%)
Bladder calculi	1 (5%)
Ureteric calculi	1 (5%)

TABLE II. *Patient characteristics*

Group	Age (yr)	Height (cm)	Weight (kg)	Sex (F/M)
Bupivacaine				
Mean	67.9	172	79.2	1/9
SEM	3.03	1.93	4.47	
n	10	10	10	
Amethocaine				
Mean	70.9	171	73.1	0/10
SEM	2.41	2.38	1.92	
n	10	10	10	

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monitored at 5-min intervals (upper arm sphygmomanometry and ECG). Respiration was observed continuously and any changes noted.

Lumbar puncture with a 25-gauge spinal needle using a standard midline approach with the patients in the lateral, horizontal decubitus position was performed via the L2–L3 or L4–L5 spaces. The spaces actually used were similar for both groups. One investigator administered the analgesia according to a randomized code, and another investigator evaluated the degree and extent of blockade.

Once a free flow of clear cerebrospinal fluid was obtained, 3 ml of either solution was injected (4–5 s ml^{-1}) without barbotage. Immediately after the injection the patient was turned supine and, 5 min later, was placed in the lithotomy position.

The cephalad spread of sensory analgesia (loss of the sensation of pin-prick) in the dependent and non-dependent sides was determined with the blunt end of a Sherwood B 400 27G/short needle at 2, 5, 10, 15, 20 and 30 min after injection, and then every 30 min.

Motor blockade in the dependent and non-dependent sides was assessed by recording the degree of motor function in the lower limbs immediately following each determination of analgesia: 0 = no paralysis (full flexion of knees and feet); 1 = inability to raise extended leg (just able to move knees); 2 = inability to flex knees (able to move feet only); 3 = inability to flex ankle joint (unable to move feet or knees).

Note was made of the operating conditions and the need for additional medication.

The patient's progress was followed into the postoperative period for signs of postspinal complications.

Statistics

Differences between means were tested for significance by Student's *t* test and differences between proportions by Fisher's exact test. Significance: $P < 0.05$.

RESULTS

Surgery

Surgery was undertaken approximately 18 min after the injection and lasted for around 1 h (table III).

Onset of sensory analgesia

The mean interval until the spread of sensory analgesia was maximal was approximately 45 min

TABLE III. *Mean values for time between administration of the local anaesthetic and the start of surgery, and the duration of the surgical procedures*

Group	Time interval inj./start of operation (min)	Duration of operation (min)
Bupivacaine		
Mean	16.4	51.8
SEM	3.08	14.0
n	10	10
Amethocaine		
Mean	17.9	51.0
SEM	1.86	9.43
n	10	10

TABLE IV. *Onset to maximum cephalad spread and duration of analgesia (means ± SEM)*

Group	Onset (min)	Duration of analgesia (min)
0.75% Bupivacaine		
Dependent	42.60 ± 7.40	293.3 ± 10.1
Non-dependent	46.60 ± 8.41	287.3 ± 7.2
0.5% Amethocaine +5% glucose		
Dependent	28.5 ± 3.95	266.5 ± 11.5
Non-dependent	28.5 ± 3.95	266.5 ± 11.5

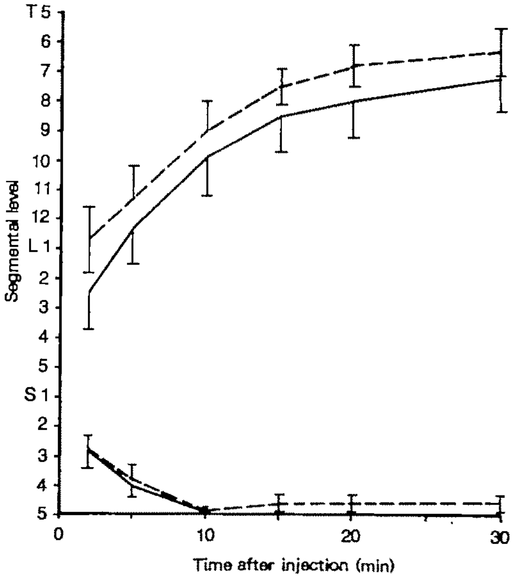

FIG. 1. Onset of analgesia (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

TABLE V. *Onset, duration and frequency of different degrees of motor blockade of the lower limbs*

	Onset (min)			Duration (min)		
Degree:	1	2	3	1	2	3
0.75% Bupivacaine						
Dependent						
Mean	4.3	6.1	8.9	294.2	281.9	270.1
SEM	0.9	0.8	2.1	10.6	11.5	13.1
n	10	10	10	10	10	10
Non-dependent						
Mean	3.9	5.7	9.3	293.1	279.3	260.7
SEM	0.9	0.6	2.3	10.7	12.2	15.1
n	10	10	9	10	10	9
0.5% Amethocaine +5% glucose						
Dependent						
Mean	5.0	5.7	9.2	218.5	195.3	175.8
SEM	1.0	1.2	1.4	19.6	17.0	21.3
n	10	10	9	10	10	9
Non-dependent						
Mean	5.5	6.2	9.6	221.0	200.8	181.1
SEM	1.3	1.5	1.4	19.2	18.2	13.0
n	10	10	7	10	10	7

for bupivacaine and 30 min for amethocaine (table IV, fig. 1) ($0.1 > P > 0.05$).

Onset of motor blockade

Mean onset time to complete motor blockade was 8–9 min for both agents (table V, fig. 2).

Spread of sensory analgesia

The mean maximum spread of sensory analgesia was similar for both agents: T6–7 (fig. 3). Bupivacaine produced significantly ($P < 0.05$) higher cephalad spread of sensory analgesia than did amethocaine 180 min after injection (fig. 3).

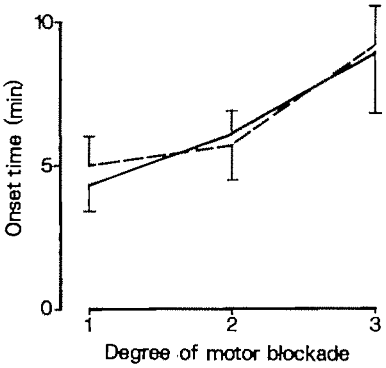

FIG. 2. Onset time to different degrees of motor blockade of the lower limbs, dependent side (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

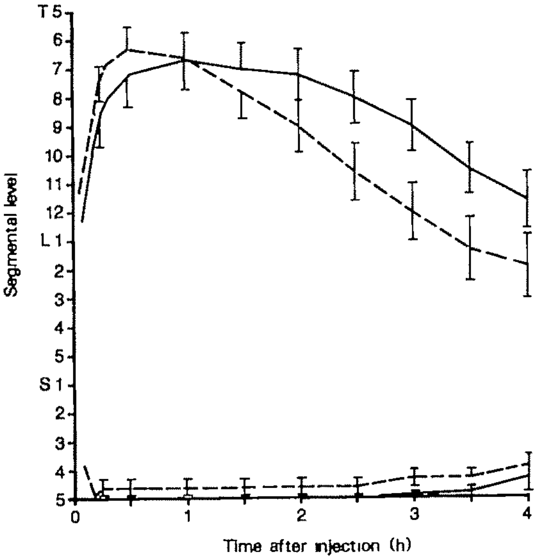

FIG. 3. Segmental spread of analgesia (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

Duration of sensory analgesia

The duration of sensory analgesia at L2 was around 4.5 and 3.5 h and at T10 around 3 and 2 h for the bupivacaine and amethocaine groups, respectively.

Significant differences were found between amethocaine and bupivacaine in the regression of

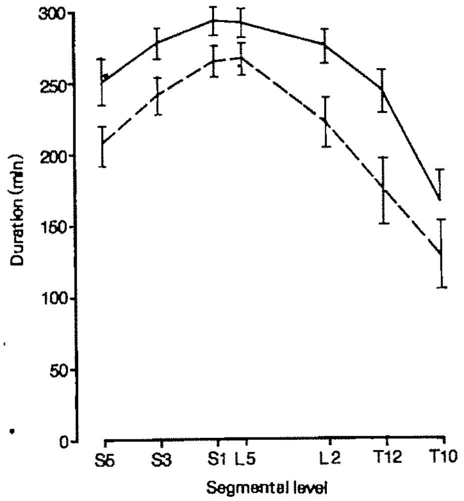

FIG. 4. Duration of analgesia at different segmental levels (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

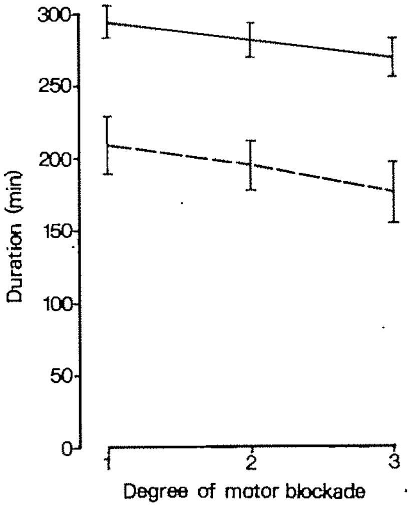

FIG. 5. Duration of different degrees of motor blockade of the lower limbs, dependent side (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

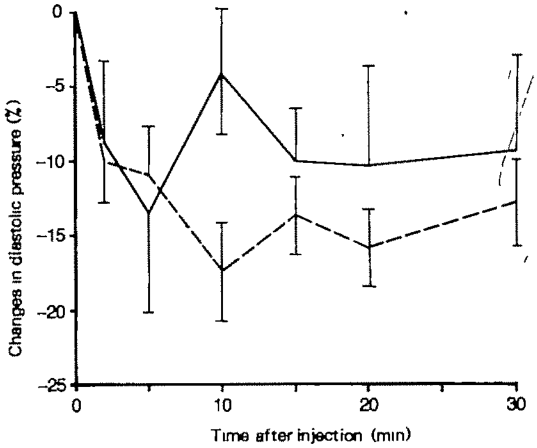

FIG. 6. Relative changes in diastolic arterial pressure during the first 30 min after injection (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

analgesia from S5 ($P < 0.05$) to S3 ($P < 0.05$) and from L2 ($P < 0.05$) to T12 ($P < 0.05$) levels (fig. 4).

Duration of motor blockade

Motor blockade of the lower limbs was complete in nine of the 10 patients given bupivacaine and in seven of the 10 patients given amethocaine (table V).

Duration of complete motor blockade of the lower limbs (degree 3) was approximately 3 h with amethocaine and 4.5 h with bupivacaine.

Significant differences were found for all degrees of motor blockade between amethocaine and bupivacaine (table V, fig. 5): degree 1, $P < 0.01$; degree 2, $P < 0.001$; degree 3, $P < 0.01$.

Quality of anaesthesia

Surgical anaesthesia was judged satisfactory in all patients.

Cardiovascular changes

The pre-anaesthetic arterial pressures and heart rates were comparable in the two groups. The mean decrease in systolic and diastolic arterial pressures was 10–15%. Heart rate decreased by 5–10%. Significant differences in changes in diastolic arterial pressure were found 10 min after the injection ($P < 0.05$). There were no significant differences in systolic arterial pressure or heart rate changes (figs 6, 7, 8). Three patients given bupivacaine and three patients given amethocaine received ephedrine because of hypotension. One patient given bupivacaine and two patients given amethocaine received atropine on account of bradycardia.

Adverse reactions

No patients developed postspinal headache.

DISCUSSION

This study was undertaken to examine the usefulness of 0.75% bupivacaine and to compare it with the more widely used amethocaine.

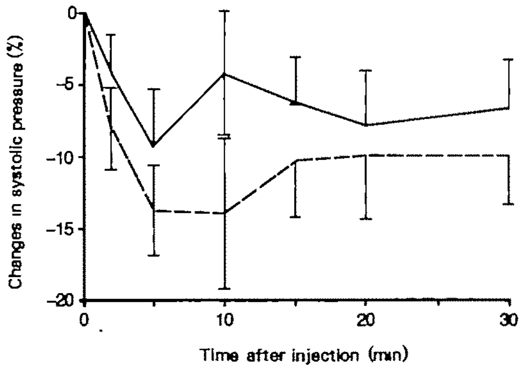

FIG. 7. Relative changes in systolic arterial pressure during the first 30 min after injection (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

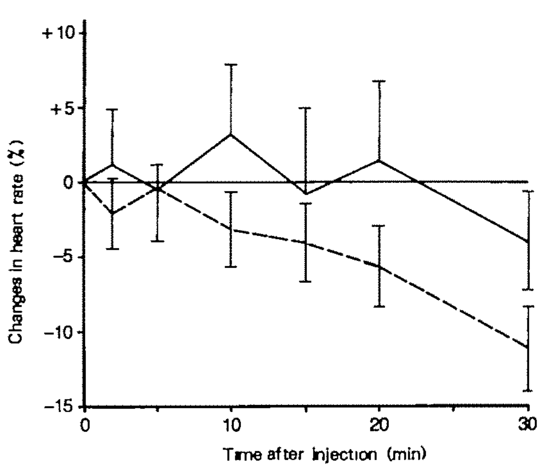

FIG. 8. Relative changes in heart rate during the first 30 min after injection (mean ± SEM). —— = 0.75% Bupivacaine; --- = 0.5% amethocaine.

The durations of sensory analgesia and motor blockade were longer in the bupivacaine group, a difference which can be explained by the use of a larger dose of bupivacaine and the use of hyperbaric amethocaine in our study. Brown and colleagues (1980) found that duration of sensory analgesia was longer with isobaric than with hyperbaric amethocaine.

There was no significant difference in onset time to maximum spread of sensory analgesia, and the mean maximum spread was similar for both agents.

The onset time to complete motor blockade was similar for both agents, but motor blockade lasted significantly longer (for all degrees of motor blockade) in the bupivacaine group. Nine of the 10 patients receiving bupivacaine and seven of the 10 patients receiving amethocaine had complete motor blockade of the lower limbs. Once again, this difference may be attributable to the higher dose of bupivacaine.

By 10 min the diastolic arterial pressure had decreased significantly more in the hyperbaric amethocaine group than in the plain bupivacaine group. There were, however, no significant differences in systolic arterial pressure or in heart rate between the groups. Chambers, Edström and Scott (1981) noted that hyperbaric 0.5% bupivacaine decreased the diastolic arterial pressure significantly more than the plain solution.

Whether the hyperbaric solution can potentiate a greater sympathetic blockade because of the hyperosmolarity, and thus greater cardiovascular changes, needs further study.

It is concluded that 0.75% plain bupivacaine 3 ml is a good alternative to hyperbaric 0.5% amethocaine with glucose in urological surgery of longer duration. The cardiovascular changes were less, and the durations of sensory analgesia and motor blockade were longer in the bupivacaine group.

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DIHYDROERGOTAMINE IN THE PREVENTION OF HYPOTENSION ASSOCIATED WITH EXTRADURAL ANAESTHESIA

M. MATTILA, P. HANNONEN, E. PUTTONEN AND S. LAPPALAINEN

SUMMARY

The efficacy of a single dose of dihydroergotamine (DHE) 0.5 mg i.v. in preventing the decrease in arterial pressure resulting from extradural anaesthesia was studied in 47 patients; 24 received DHE and 23 a placebo, in a randomized double-blind manner. Although the decrease in systolic arterial pressure was more pronounced in the placebo group than in the DHE group, the difference was not significant. Diastolic and mean arterial pressures were both significantly lower in the placebo group than in the DHE group during the initial phase of extradural anaesthesia. Administration of DHE did not cause any significant changes in heart rate. In both groups the heart rate decreased significantly during the 5-h period following the induction of extradural anaesthesia. The patients in the placebo group needed additional medication to increase unacceptably low arterial pressures or heart rate more frequently than the patients in the DHE group.

Extradural anaesthesia produces regional preganglionic sympathetic blockade and causes dilatation of both resistance and capacitance vessels. Consequently, systemic arterial hypotension is a frequent side-effect of extradural anaesthesia, often despite the administration of a fluid preload (Zaaijman and Slabber, 1978).

Dihydroergotamine (DHE) constricts the capacitance vessels by stimulating the alpha-adrenoceptors. As a result of its tonic effect on limb veins, venous return is increased and venous pooling prevented (Berde, Schild and Weil, 1981). In addition, it has been shown that DHE restores the arterial pressure, by increasing the systemic vascular resistance, in areas subject to sympathetic blockade (Mellander and Nordenfelt, 1970; Bergenwald et al., 1972; Castenfors, Lindblad and Mortasawi, 1975; Hilke et al., 1978; Reichelt et al., 1980; Bergenwald et al., 1981). On account of these characteristics and its prolonged duration of action, DHE could have a role in the prevention of the vasodilatation caused by extradural blockade.

We have performed a randomized, placebo-controlled double-blind study which investigated the clinical efficacy of DHE in the prevention of the arterial hypotension associated with extradural anaesthesia.

PATIENTS AND METHODS

Patients

The number and characteristics of the 47 patients included in the study are detailed in table I. There were no significant ($P > 0.1$) differences between the two groups of patients in respect of sex ratio, age, weight or height. All required surgery for minor orthopaedic trauma, excision of varicose veins or herniorrhaphy. Pregnant patients, and those suffering from coronary insufficiency or uncontrolled hypertension, were excluded. The study was approved by the Ethics committee of the University Central Hospital of Kuopio and the patients gave their informed consent.

Following premedication (flunitrazepam 0.2–0.4 mg) the patients were randomly allocated to two groups, to receive either dihydroergotamine (Orstanorm, Sandoz) 0.5 ml of a 1-mg ml^{-1} solution ($n = 24$) or a placebo (0.9% sodium chloride solution 0.5 ml; $n = 23$). Both solutions were administered i.v. as a single bolus.

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TABLE I. *Patient data*

	Dihydro-ergotamine	Placebo
No. of patients	24	23
Sex (female/male)	13/11	8/15
Age (yr)		
Mean ± SD	35.8 ± 10.3	41.7 ± 12.9
Range	17–53	21–62
Weight (kg) (mean ± SD)	72.7 ± 10.9	72.9 ± 11.8
Height (cm) (mean ± SD)	168.1 ± 6.8	169.8 ± 9.2

Extradural anaesthesia

Approximately 5 min later lumbar extradural anaesthesia was initiated with a single injection of 20 ml of 0.5% bupivacaine with adrenaline (bupivacaine 5 mg ml^{-1} + adrenaline 5 µg ml^{-1}) plus 5–10 ml of lignocaine with adrenaline (lignocaine 10 mg ml^{-1} + adrenaline 10 µg ml^{-1}). The lumbar puncture was performed with the patient in the sitting position, the patient being placed supine immediately after the injection of the local anaesthetics.

Measurement of arterial pressure and heart rate

Arterial pressure and heart rate were measured using an automatic sphygmomanometer (Sentron, Bard) and recorded every 2 min during the first 30–60 min and then at 5- to 15-min intervals for up to 3–5 h. Before the administration of DHE or placebo, two baseline measurements were obtained with the patient in the supine position. The next recordings of arterial pressure and heart rate were performed with the patient in the sitting position. Thereafter, all measurements were performed with the patient supine. The use of the same automatic device for the measurement of systolic, diastolic and mean arterial pressures and heart rate minimized the possible variability between individuals and between apparatus.

Fluid infusions and additional medication

On the day of operation 2000–3000 ml of 5% dextrose + 0.3% sodium chloride was infused. However, if there was a significant decrease in systolic arterial pressure (−30 mm Hg or more) after the induction of extradural anaesthesia, a further dose of DHE or placebo (according to the code) was administered. If no effect was achieved, etilefrine-HCl 2 mg (Effortil) was given i.v. In addition, gelatine hydrolysate 500–1000 ml (3.5% Haemaccel) was used as volume substitute.

If the patient received etilefrine, any records of arterial pressure and heart rate obtained during the succeeding 10 min were excluded from the results of the study. If the heart rate decreased to less than 60 beat min^{-1}, glycopyrrolate 0.2 mg or atropine 0.5 mg was given i.v.

Statistics

For the statistical evaluation Chi-square test, Student's t test for paired and independent samples and Wilcoxon's rank sum test were applied.

RESULTS

Systolic, diastolic and mean arterial pressures

Changes in systolic, diastolic and mean arterial pressures are shown in figures 1, 2 and 3, respectively.

The initial arterial pressures in the DHE and placebo groups were comparable. There were no statistically significant differences between the two groups in systolic pressure during the entire period of the study. Over the period 20–45 min, diastolic and mean arterial pressures were significantly ($P < 0.001$) lower in the placebo group than in the DHE group.

The administration of DHE or placebo did not cause any immediate change in arterial pressure. Following the initial change from the supine to the sitting position, there was a significant increase in the diastolic ($P < 0.01$) and mean ($P < 0.05$) arterial pressures in the placebo group, whereas in the DHE group this increase was significant ($P < 0.01$) in the case of the mean arterial pressure only. The return to the supine position was accompanied by a significant ($P < 0.001$) decrease in the systolic, diastolic and mean arterial pressures in both groups if one compares the values obtained at 20–45 min with the baseline values. In six patients (26%) in the placebo group and one patient (4%) in the DHE group, systolic pressure decreased to less than 100 mm Hg during this period (20–45 min). Diastolic pressure decreased to less than 60 mm Hg in 19 patients (83%) in the placebo group and in nine patients (39%) in the DHE group ($P < 0.01$). The mean arterial pressure decreased to less than 75 mm Hg in 18 patients (78%) in the placebo group and in nine patients (39%) in the DHE group ($P < 0.05$).

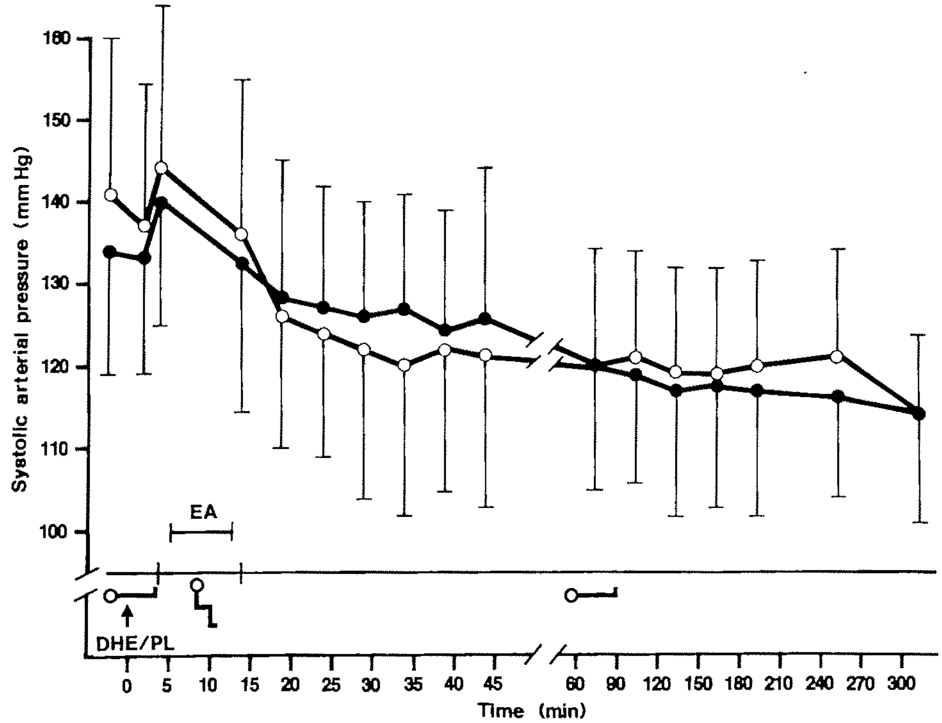

FIG. 1. Mean (± standard deviation) systolic arterial pressure. There were 24 patients in the dihydroergotamine (DHE) group (●) and 23 patients in the placebo (PL) group (○). EA indicates the time period for the induction of extradural anaesthesia. The arrow indicates the time point of the administration of DHE or PL. ○—┘ indicates the supine or sitting position of the patient. Note the change in time scale at 60 min.

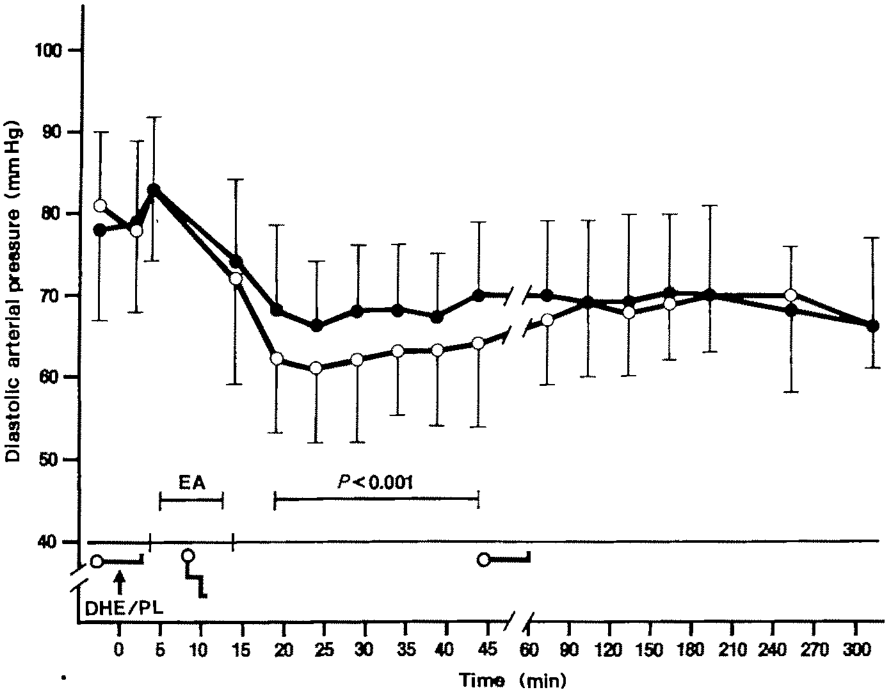

FIG. 2. Mean (± standard deviation) diastolic arterial pressure. Details as for figure 1.

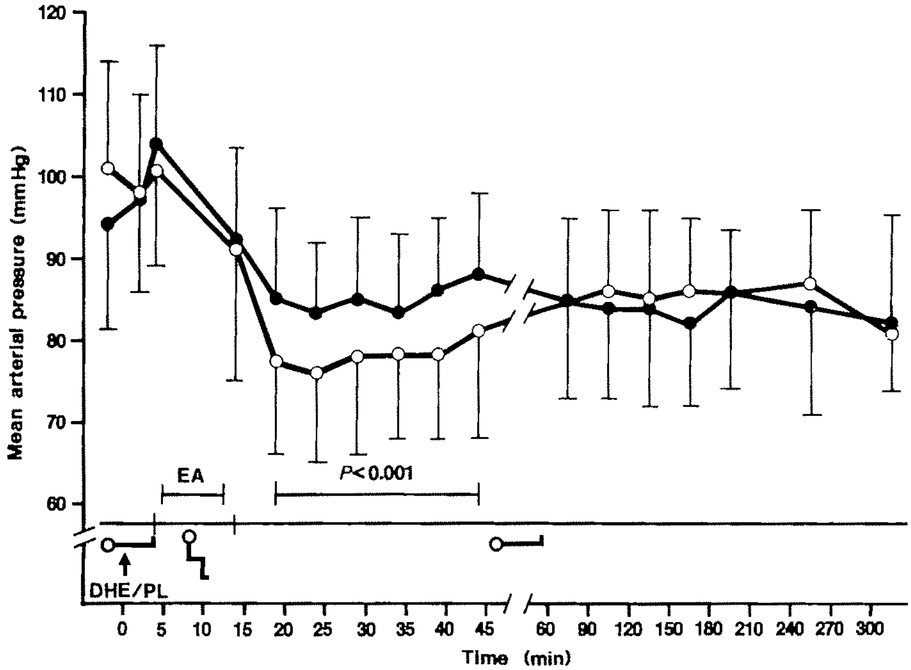

FIG. 3. Mean (± standard deviation) mean arterial pressure. Details as for figure 1.

In the DHE group there was a further significant ($P < 0.001$) decrease in systolic arterial pressure during the 60–300-min period as compared with the 20–45-min period, whereas in the placebo group no further decrease occurred during the later period. In the DHE group the diastolic and the mean arterial pressures remained stable from 20 to 300 min, whereas in the placebo group there was a significant ($P < 0.001$) increase in both diastolic and mean arterial pressures, from the value obtained during the 20–45-min period to the value obtained later (60–300 min).

Heart rate

Figure 4 shows the average changes in heart rate. The initial value was greater ($P < 0.02$) in the DHE-group than in the placebo group. During the 20–45-min period heart rate was significantly ($P < 0.001$) lower in the placebo group than in the DHE group. For the 60–300-min period no statistically significant differences in heart rate could be demonstrated between the groups.

The administration of placebo or DHE did not cause any immediate change in heart rate. Although there was an increase in heart rate following the change from the supine to the sitting position, the average increase was not significant in either group. No significant changes could be observed in either of the groups between the initial values of heart rate and the value obtained for the period 20–45 min. During the 20–45-min period there were four patients (17%) in the placebo group and one patient (4%) in the DHE group in whom the heart rate was less than 60 beat min^{-1}. Comparison of the heart rates in the 20–45-min period with those in the later period demonstrated that there was a significant ($P < 0.001$) overall decrease from 76 to 69 beat min^{-1} in the placebo group and from 81 to 68 beat min^{-1} in the DHE group.

Additional medication

Table II depicts the number of occasions on which additional medication was required because of a decrease in systolic arterial pressure. In the DHE group, three patients (13%) experienced a decrease in systolic pressure of 30 mm Hg or more. However, this decrease could be corrected in all three patients by giving the second dose of DHE. In contrast, in the placebo group, eight patients (35%) were given a second dose of placebo and because of a lack of effect, five patients (22%) were given etilefrine and five patients gelatine hydrolysate. Two of these patients were given both etilefrine and gelatine hydrolysate.

Twelve patients (52%) in the placebo group and

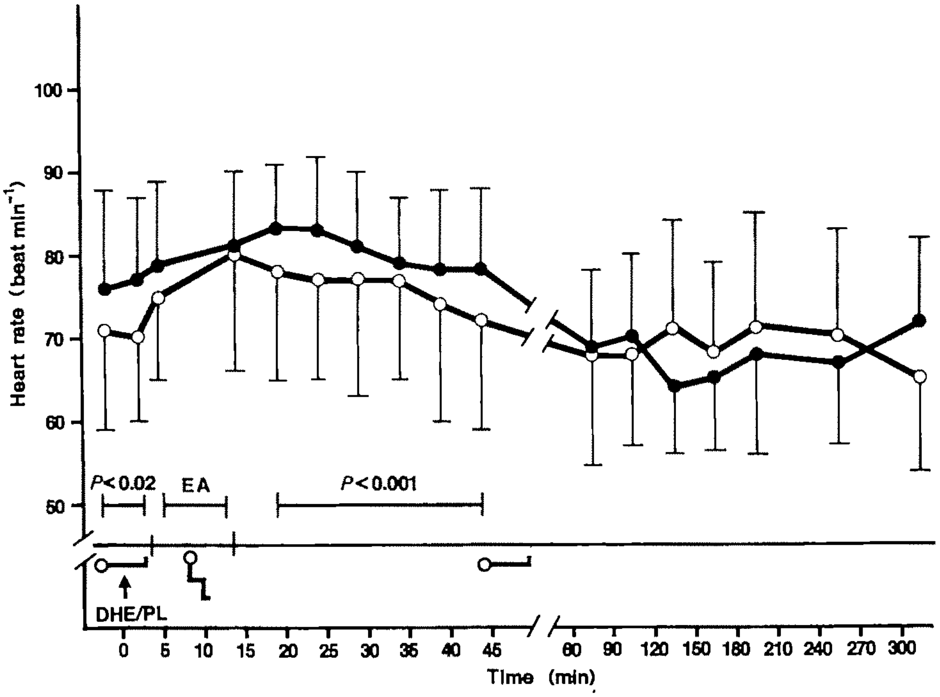

FIG. 4. Mean (± standard deviation) heart rate. Details as for figure 1.

TABLE II. *Additional medication the patients received to compensate for a decrease in systolic arterial pressure of 30 mm Hg or more after the induction of extradural anaesthesia. DHE = dihydroergotamine; PL = placebo. Values are number of patients (%)*

	DHE group	PL group
Second dose of DHE or PL	3 (12.5%)	8 (34.8%)
Etilefrine-HCl	0 (0.0%)	5 (21.7%)
Gelatine hydrolysate	0 (0.0%)	5 (21.7%)
Atropine–glycopyrrolate	6 (25.0%)	12 (52.0%)

six (25%) in the DHE group received either glycopyrrolate 0.2 mg or atropine 0.5 mg i.v. to correct a heart rate of less than 60 beat min^{-1}.

DISCUSSION

Since both groups of patients received the same doses of local anaesthetic agents by the same route, the possible circulatory effects of adrenaline and other components in the local anaesthetics (Bonica et al., 1971) should have no influence on the comparison between the effects of DHE and placebo.

Following the induction of extradural anaesthesia there was the typical decrease in the systolic arterial pressure in both groups, although the decrease was more pronounced in the placebo group. The mean decreases in diastolic and mean arterial pressures were significantly ($P < 0.001$) smaller in the DHE group than in the placebo group during the initial phase of the extradural anaesthetic.

Although systolic arterial pressure is the most commonly used index for monitoring the circulation, it does not seem to be the most sensitive. Our results indicate that the diastolic and mean arterial pressures are more sensitive indicators of changes in the circulation.

One clinically important finding was that, in the placebo group, 26% of the patients experienced an unacceptably low systolic pressure (< 100 mm Hg) during the 30 min which followed the induction of the extradural anaesthesia, whereas the respective figure in the DHE group was 4%. In the placebo group 83% of the patients experienced a decrease in diastolic pressure to a value of less than 60 mm Hg, the corresponding proportion of patients in the DHE group being 39% ($P < 0.01$). Since diastolic pressure is important as far as the coronary circulation is concerned, DHE may be beneficial from this point of view.

Since the initial values of heart rate differed significantly between the two groups, the changes cannot be discussed realistically. No anticholinergic drugs were used in premedication although, if the heart rate did decrease to less than 60 beat min^{-1}, either glycopyrrolate or atropine was given. The patients in the DHE group needed less anticholinergics than the patients in the placebo group. This further supports the view of the stabilizing effect of DHE. The effect of the anticholinergics explains the paradoxical course of the heart rate in the later observation period.

In the present study the prophylactic use of DHE decreased the number of untoward circulatory episodes and the need for additional medication (table II). In practice this means a more stable anaesthetic, without sudden changes in circulatory indices connected with unpleasant subjective sensations by the patient.

Since a part of the patient is capable of compensating intrinsically for the circulatory changes induced by the extradural anaesthesia, the anaesthetist tends to treat them symptomatically. There are several different methods of compensating for the vasodilatatory effects of extradural anaesthesia, for example volume substitution, where a colloidal solution has been shown to be more effective than a crystalloid solution (Koski et al., 1984). Another approach is to counteract the vasodilatation with vasoconstrictor drugs given either prophylactically or in response to the symptoms of inadequate perfusion. In the present study etilefrine was given as short-term treatment, whereas gelatine was used to achieve a more prolonged effect.

The aim of the present investigation was to evaluate the efficacy of DHE in the prophylaxis of circulatory changes resulting from extradural anaesthesia. In the dosage used in this study DHE has a tonic effect on capacitance vessels only (Berde, Schild and Weil, 1981) with the exception of those areas subjected to sympathetic blockade, where it restores the arterial pressure by increasing peripheral resistance (Castenfors, Lindblad and Mortasawi, 1975). Hence, DHE is preferable to arterial vasoconstrictors like etilefrine. Previous studies have shown that DHE 0.5 mg given i.m. (Mühe et al., 1975) or s.c. (Lindblad, Abisch and Bergqvist, 1983) had a tonic effect on capacitance vessels which lasted for 12 h. However, when given i.m. or s.c., DHE takes 1–2 h to reach its peak plasma concentration. When it is given i.v., a more rapid effect is achieved (Hilke et al., 1978). Although DHE 0.5 mg i.v. was superior to placebo in counteracting the circulatory effects of the extradural anaesthesia, it was not possible with this dose to eliminate totally the changes in circulatory variables. Thus, in order to prolong the action of DHE it might be preferable to use a higher dose, for example 1 mg, given either in one bolus dose or divided into two doses of 0.5 mg each given with an interval of about 10–20 min.

In conclusion, the prophylactic prevention of vasodilatation as a result of extradural anaesthesia can be justified, because in the placebo group the decrease in arterial pressure after the induction of the blockade was marked and the need for additional medication obvious. By the prophylactic use of DHE 0.5 mg the decrease in arterial pressure and the need for additional medication could be decreased significantly. However, it is important to note that DHE should not be given after a massive volume substitution with crystalloids, as this may result in pulmonary oedema. In the present study diastolic and mean arterial pressures were found to be more sensitive indicators of changes in arterial pressure than the systolic pressure.

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THERMOREGULATORY RESPONSES TO COOLING IN PATIENTS SUSCEPTIBLE TO MALIGNANT HYPERPYREXIA

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SUMMARY

The influence of 1 h of surface cooling on body temperature, variables which contribute to thermoregulation and selected hormones and metabolites has been investigated in seven patients susceptible to malignant hyperpyrexia (MH) and in seven matched control subjects. Cooling was achieved using a liquid conditioned coverall worn next to the skin. Skin temperature decreased similarly in both groups of subjects. Heat production increased in both groups, with a slightly higher heat production being seen in the MH group. Core temperature increased in both groups of subjects at the start of the cooling period, with a significantly greater increase occurring in the MH group (control: +0.13 ± 0.13; MH: +0.28 ± 0.10 °C, $P < 0.05$). There were no significant changes in plasma lactate, or pyruvate concentrations. Plasma glucose concentrations were lower in the control group; after 30 min of cooling plasma glucose was 4.25 ± 0.37 mmol litre^{-1} in the control group and 5.34 ± 0.21 mmol litre^{-1} in the MH group ($P < 0.05$). There were no significant changes in plasma thyroxine or adrenaline concentrations. Plasma noradrenaline increased in both groups of subjects. The increase in plasma noradrenaline of the MH patients was greater than in most of the control subjects.

Predisposition to malignant hyperpyrexia (MH) is encountered as a dominant pharmacogenetic abnormality in a small proportion of patients undergoing anaesthesia with a variety of commonly used anaesthetic agents.

The primary cause of the disease has not yet been established. In pigs MH is associated with an increased activity of the sympathetic nervous system (Gronert, Milde and Theye, 1977). Differences in metabolic heat production and circulating concentrations of hormones (insulin, thyroxine and cortisol) and metabolites (triglycerides, lactate and pyruvate) have been observed in MH-susceptible individuals during moderate exercise and following a test meal when compared with controls (Campbell, Ellis and Evans, 1981). The differences described in man in the latter study could also be explained by a more active sympathetic nervous system.

Release of noradrenaline from sympathetic nerve terminals (and, probably, release of adrenaline from the adrenal medulla) contributes to the cardiovascular and metabolic adjustments necessary to reduce heat loss in the cold. Therefore, it seemed reasonable that, if MH-susceptible individuals have a stress-induced overactivity of the sympathetic nervous system, they will display a greater tolerance to cold when compared with non-susceptible individuals.

In the conscious subject the major cardiovascular change essential for maintaining body temperature in the cold is a redistribution of blood from the periphery to the core. This is achieved through cutaneous vasoconstriction mediated by α-adrenoceptors (Rowell, 1977). There is a concurrent increase in heat production. Muscle tone is increased until shivering develops. One of the factors essential for sustained shivering is an adequate transport of blood glucose across the cell membrane into muscle (Therminarius et al., 1979). Adrenaline may indirectly increase the supply of glucose to shivering muscles as a result of its effects on the release of glucagon from the pancreas and of glycerol from adipose tissue.

If sympathetic nervous activity (and the release of adrenaline) is augmented in the cold in MH-susceptible individuals, a more intense peripheral vasoconstriction and a decrease in heat

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loss should be seen. This could occur even with a higher metabolic heat production, as the two mechanisms are not directly linked and use different adrenergic receptors.

The present study was designed to investigate whether there were any differences, in body temperature, peripheral blood flow and heat production during cooling, between individuals susceptible to MH and non-affected controls.

SUBJECTS, PATIENTS AND METHODS

Fourteen male volunteers gave written informed consent to take part in the study, which was approved by the Clinical Research (Ethics) Committee of Leeds Eastern District Health Authority. Seven of the volunteers were patients who had previously attended the University of Leeds Malignant Hyperpyrexia Investigation Unit at St James' University Hospital for a screening procedure. The screening procedure involves a muscle biopsy of the vastus internus muscle followed by an *in vitro* investigation of the living muscle tissue, which is challenged by known trigger agents including halothane and caffeine (European Malignant Hyperpyrexia Group, 1984). All had been shown to be MH-susceptible. The control subjects had not undergone muscle biopsy but, in view of the rarity of the disease, were assumed to be insusceptible. The ages, body weights and percentages of body fat, calculated from measurements of skinfold thickness, of the control and MH groups were similar. Skinfold thickness was measured at four sites: biceps, triceps, subscapular and suprailiac. Body density and percentage body fat were calculated from the formula of Durnin and Womersley (1973). The subjects were aged 18–40 yr, their heights were 1.689–1.829 m, weights 60.4–85.9 kg and their percentages body fat were 9.2–21%.

The studies were carried out in a laboratory initially set at 24 °C, although the ambient temperature increased gradually during each investigation, but by not more than 2 °C on any occasion. The subjects were cooled using a liquid conditioned coverall (LCC) (RAF Institution of Aviation Medicine), worn next to the skin. The LCC is made of stretch fabric with polyvinyl chloride tubing stitched within cloth tunnels. A dilute mixture of antifreeze was distributed first to the wrist and ankles, then over the limbs and finally to the torso before being returned to the pump (Churchill), which was designed to maintain a constant rate of flow through the system. The temperature of the fluid entering the suit at the start of the cooling period was 25.0±0.3 °C in the control group and 25.3±0.4 °C (SEM) in the MH group. The LCC inlet temperature was decreased gradually over the following 30 min to 14.1±0.6 °C in the control group and to 14.9±0.7 °C in the MH group. The suit inlet temperature was maintained as closely as possible to this temperature for the following 30 min.

Approximately 45 min before the start of cooling a cannula was inserted to a left antecubital vein and was flushed with physiological saline. All subjects were given a standard 1348-kJ meal (milk-based drink) mid-morning at least 2 h before the start of the cooling.

The design of the study comprised a 30-min control period, a 60-min period of cooling and a 30-min recovery period. Core temperature was measured using a thermistor embedded in a plastic earmould. The earmould was inserted to the right external auditory meatus with the thermistor protruding 4 mm from the inner edge of the earmould. It was insulated using foam padding and a bandage. Skin temperature was measured at four sites: the chest (overlying the second intercostal space to the left of the sternum), ventral surface of the mid-forearm, antero–lateral surface of the thigh and antero–medial aspect of the mid-calf.

Mean skin temperature was calculated using the formula of Ramanathan (1964). These temperatures and the inlet and outlet temperatures of the suit were monitored using an Edale thermometer (Model C, Edale Instruments, Cambridge). All temperatures, including ambient temperature were recorded at 2-min intervals throughout the study.

Expired air was collected for 4 min in each 10-min period via a low resistance mouthpiece (Hans Rudolph, Kansas City) into a Douglas bag. It was analysed for oxygen concentration using a paramagnetic oxygen analyser (Servomex OA 252); the volume was measured using a Tissot spirometer (all measurements were corrected to STPD). Heat production was calculated using the formula of Weir (1949). Shivering was noted, but no qualitative recordings of electromyographic activity were made.

Pulse rate and arterial pressures (by upper arm sphygmomanometry) were measured at the same time as each measurement of peripheral blood flow.

Just preceding each collection of expired gas, blood samples were taken for the determination of the plasma concentrations of glucose, lactate, pyruvate, thyroxine and catecholamines. Plasma glucose, lactate and pyruvate concentrations were measured using commercially available kits (Boehringer, Mannheim). Plasma thyroxine concentration was measured by radioimmunoassay. Plasma concentrations of the catecholamines were measured by high pressure liquid chromatography using the technique described by Hjemdahl, Daleskog and Kahan (1979).

The catecholamine extractions were carried out using acid-washed alumina. The HPLC system comprised a pump (ACS HPLC model 300), a valve injector with a 100-µl injection loop (Rheodyne 7125), a 25 × 4.6-cm column (Spherisorb 5 ODS 2; Technicol) and an electrochemical detector (Bioanalytical Systems LC 4A). The current generated by the oxidation of the catecholamines was monitored using a potentiometric recorder (Omniscribe B500, Houston Instruments). The catecholamines were separated on the column using a mobile buffer containing 100 ml of $NaH_2PO_4 \cdot 2H_2O$ 1.0 mol $litre^{-1}$ and Na EDTA 100 mmol $litre^{-1}$ made up to 1 litre with nanopure water. To this 0.216 g of 1-octane sulphuric acid was added. The solution was filtered through a 0.2-µm membrane filter before methanol 60 ml was added. The mobile phase was helium-degassed and the pH adjusted to 3.2 with NaOH or H_3PO_4.

The flow rate through the system was set at 0.8 ml min^{-1} as this gave good separation of the peaks. The effluent from the column passed into a low volume, thin-layer cell containing a carbon paste electrode. A potential of +0.65 V was held between this electrode and the silver-silver-chloride reference electrode which oxidized the catecholamines, then it was amplified and the voltage output from this electrode was transmitted to the chart recorder. The concentration of the catecholamines (or other electrically active chemicals in the effluent) is proportional to the electrolysis current generated. The voltage output was regulated at 2 V per nA of current generated. A chart running speed of 0.1 cm min^{-1} was used.

All results are expressed as mean ±SEM. Statistical significance was determined using Student's t test.

RESULTS

Shivering

Signs of shivering were observed in half the subjects overall, with a similar incidence in both groups. In the control group no shivering was observed in three subjects; in one subject slight shivering was noted; in two subjects shivering was pronounced and the seventh subject shivered shortly after the investigation had ended. In the MH group no shivering was observed in four subjects, but three subjects visibly shivered. All subjects reported that they felt cold, but all were willing to complete the test.

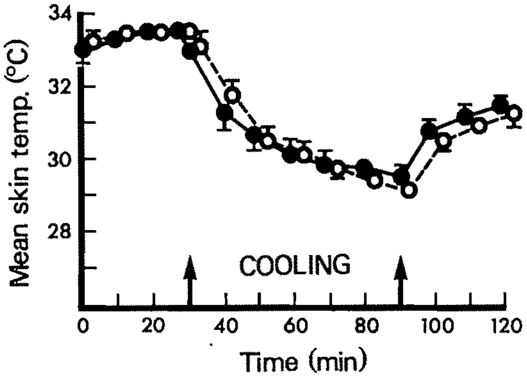

FIG. 1. The influence of surface cooling on skin temperature in patients susceptible to malignant hyperpyrexia (○) compared with control subjects (●).

Body temperature

Skin. Skin temperature decreased similarly in both groups (fig. 1). This occurred despite differences in the suit outlet temperatures between the groups after the start of cooling.

External auditory meatal. Core temperature changes are shown in figure 2. Thirty minutes after the start of cooling, core temperature had increased in both groups with a greater increase occurring in the MH group (+0.31±0.13 compared with 0.10±0.13 °C in the control group) ($P < 0.05$) at 60 min. Subsequently, core temperature decreased in both groups. Overall core temperature decreased from 36.77±0.08 to 36.37±0.10 °C in the control group and from 36.54±0.14 to 36.46±0.15 °C in the MH group (ns).

Thermodynamics

Indirect calorimetry. The changes in heat production are shown in figure 3. Heat production increased in both groups in response to cooling. Heat production increased to a greater extent overall in the MH group. In the control group, heat production increased from a baseline measurement of 5.55±0.37 kJ min^{-1} to a peak of

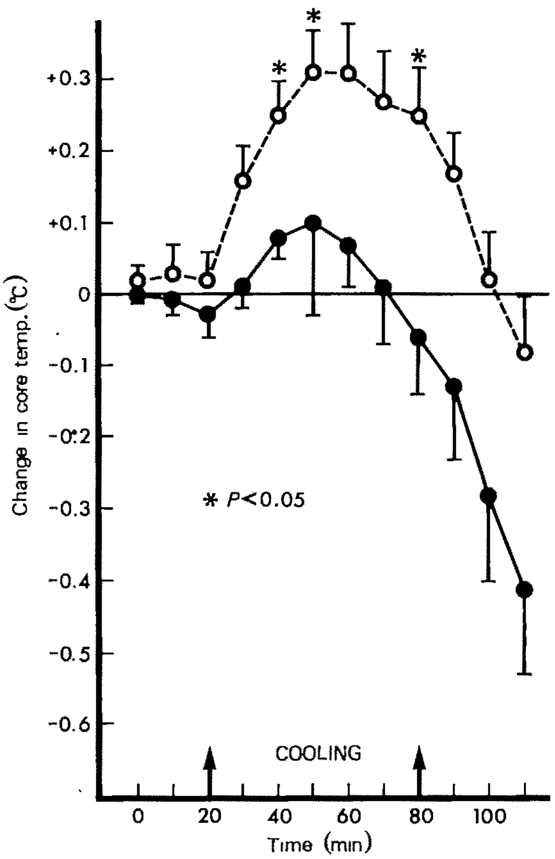

FIG. 2. The influence of surface cooling on external auditory meatal temperature in patients susceptible to malignant hyperpyrexia (○) compared with control subjects (●).

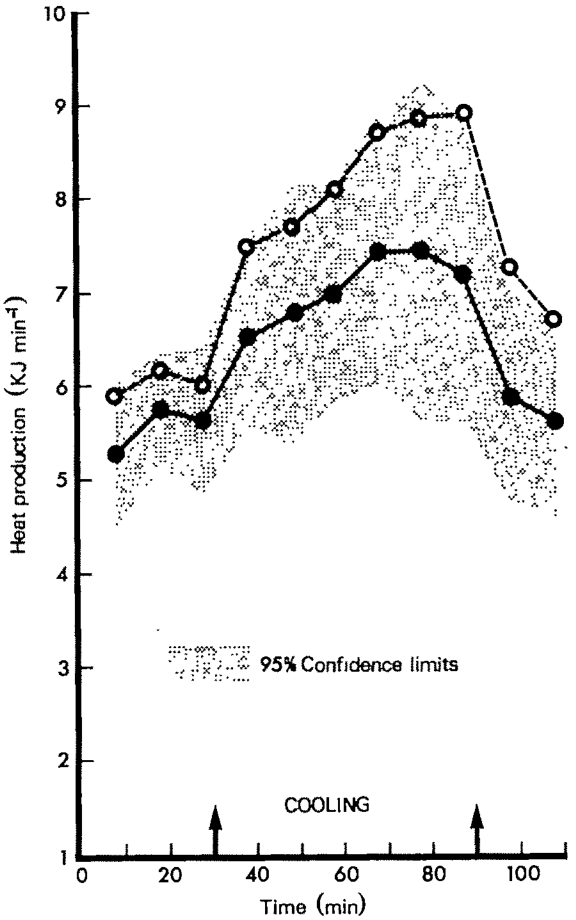

FIG. 3. The influence of surface cooling on heat production in patients susceptible to malignant hyperpyrexia (○) compared with control subjects (●).

7.44±0.93 kJ min^{-1} 45–50 min after the start of cooling. In the MH group, heat production increased from 6.02±0.50 kJ min^{-1} to a peak of 8.91±0.95 kJ min^{-1} after 55–60 min of cooling.

Heat transfer. After 30 min of cooling, the difference between inlet and outlet temperature of the suit was 5.1±1.1 °C in the control group and 3.1±0.9 °C in the MH group (ns) (fig. 4).

Heart rate and arterial pressure

Heart rate decreased during cooling in both groups. In the control group heart rate decreased from 70±5 beat min^{-1} to 59±4 beat min^{-1} and similarly, in the MH group, from 67±4 beat min^{-1} to 59±3 beat min^{-1} at the end of the study.

Arterial pressure increased slightly in both groups. In the control group it increased from 118±2 (systolic) and 72±4 mm Hg (diastolic) to 129±4 and 85±4 mm Hg, respectively, at the end of cooling. In the MH group arterial pressure increased from 123±3 (systolic) and 68±3 mm Hg (diastolic) to 132±3 and 80±2 mm Hg, respectively.

Clinical biochemistry

The main findings are summarized in table I.

Plasma glucose concentration. Plasma glucose concentration decreased during the study in both groups. In the control group it decreased from a mean resting value of 5.21±0.57 mmol litre^{-1} to 4.25±0.37 mmol litre^{-1} after 30 min of cooling. In the MH group the decrease in plasma glucose concentration was less marked, decreasing from a mean resting value of 5.89±0.41 mmol litre^{-1} to

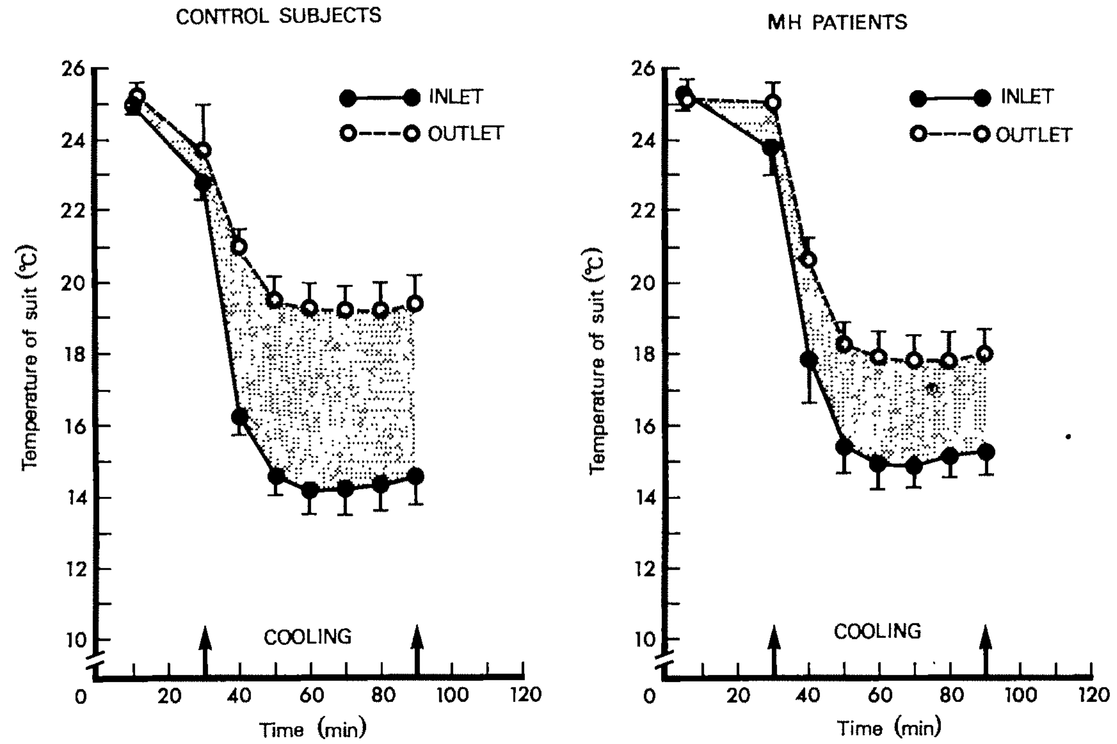

FIG. 4. The influence of surface cooling on heat transfer in control patients and those susceptible to malignant hyperpyrexia.

TABLE I. *Summary of clinical biochemistry (mean values ±SEM). †Control data after elimination of one subject by Chauvenet's criterion (see text).* n = 7. *P < 0.05; **P < 0.01

	Baseline	Cold-stress	Cold-stress	Recovery
Time (min)	0	30	60	90
Glucose (mmol litre^{-1})				
Control	5.21±0.57	4.25±0.37	4.38±0.36	4.47±0.16
MH	5.89±0.41	5.34±0.21*	4.96±0.19	4.92±0.15
Lactate (mmol litre^{-1})				
Control	2.01±0.24	1.69±0.98	1.51±0.25	1.56±0.34
MH	2.37±0.35	2.54±0.39	2.42±0.28	2.01±0.27
Pyruvate (μmol litre^{-1})				
Control	39±5	49±3	43±6	48±9
MH	56±10	44±5	48±4	41±3
Thyroxine (mmol litre^{-1})				
Control	87±5	90±5	90±5	90±6
MH	81±5	82±5	83±5	82±4
Catecholamines				
Time (min)	0	40	60	90
Adrenaline (nmol litre^{-1})				
Control	0.44±0.11	0.32±0.07	0.25±0.07	0.26±0.10
MH	1.32±0.23**	0.75±0.28*	0.75±0.14**	0.59±0.07*
Noradrenaline (nmol litre^{-1})				
Control	2.69±0.50	4.03±1.21	5.67±1.58	3.99±1.21
†Control	2.34±0.43	2.89±0.48	4.13±0.40	2.89±0.60
MH	4.91±1.12	6.49±0.79**	7.60±0.81**	5.15±1.02

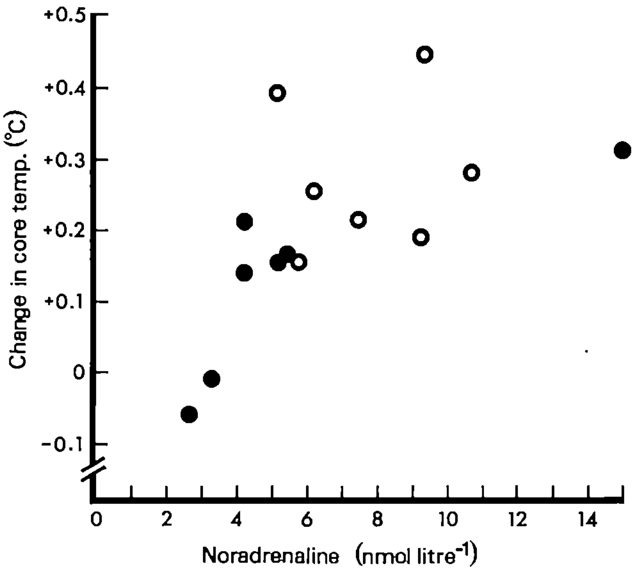

FIG. 5. The relationship between plasma noradrenaline and core temperature during surface cooling in patients susceptible to malignant hyperpyrexia (○) compared with control subjects (●).

5.34 ± 0.21 mmol litre^{-1} after 30 min. The plasma glucose concentrations of the two groups were significantly different after 30 min of cooling ($P < 0.05$). There were no statistical differences in plasma glucose concentration between the groups at other times during the study.

Plasma lactate and pyruvate concentrations. There were no changes in plasma concentrations of either lactate or pyruvate in either group during the study; the values were similar in both groups.

Plasma thyroxine concentration. There were no changes in plasma thyroxine concentration in either group during the study. The values were similar in both groups.

Plasma catecholamine concentrations. (i) Adrenaline: Plasma adrenaline concentrations were higher in the MH group throughout the study. They decreased slightly in both groups during the cooling period. (ii) Noradrenaline: Plasma noradrenaline concentration increased during cooling in both groups of subjects. The subjects who had the higher circulating noradrenaline concentrations tended to have the higher core temperatures at the end of the cooling period (fig. 5).

It can be seen from figure 5 that the control subject who had the highest core temperature (in relation to his baseline temperature) after 60 min of cooling had a remarkably high circulating noradrenaline concentration. Using Chauvenet's criterion, it is permitted to recalculate the data without the extreme value (providing the extreme value lies more than three times the standard deviation of the mean of the group away). After elimination of the extreme value, the circulating noradrenaline concentrations of the control subjects become significantly lower than the MH group (see table I).

DISCUSSION

The occurrence of MH during anaesthesia is well documented. The clinical observation of an MH episode in man suggests a higher level of sympathetic nervous activity in MH-susceptible individuals (Gronert, 1980). However, the higher level of sympathetic activity may well be a reaction secondary to a process somewhere else in the body. It is possible that this site is within skeletal muscle, since local Ca^{2+} concentrations are presumed to be high in the muscle of MH-susceptible patients during an episode (Moulds, 1975). Recently, the integrity of the sarcolemma has been questioned, as an important source of ionic calcium could be from the extracellular fluid; a malfunctioning sarcolemma leaking calcium down its concentration gradient would result in the high intracellular concentrations envisaged (Gronert, 1980). In addition, the sarcolemma can be presumed to contain adrenoceptors which would also be affected by an abnormal sarcolemma. Yet it seems unlikely that the sympatho–adrenal axis is the primary cause for the abnormal muscle response to the triggerring agents, since neither alpha- nor nonselective (β_1 and β_2) beta-blockade prevents the former response during a standard suxamethonium challenge of two 50-mg doses in the Pietran pig (Lister, Hall and Lucke, 1976). However, the alpha-adrenoceptors do appear to mediate some of the responses associated with a fully developed episode of MH.

The small increase in heat production and the slightly lower heat loss of the MH patients observed in the present study are consistent with the increases in the circulating noradrenaline concentration which occurred during cooling when compared with the controls. In this respect the results of the present study support earlier observations of sympathetic overactivity in pigs (Gronert, Milde and Theye, 1977). However, some of the subjects shivered and as the degree of shivering, which was not quantified, must have varied between individuals, the muscular activity would affect heat production and noradrenaline release differently. Thus, it is possible that shivering, rather than MH, explains the differences in heat production and noradrenaline concentration observed between the two groups.

The secretion of adrenaline from the adrenal medulla is usually stimulated in the same direction as noradrenaline secretion from sympathetic post-ganglionic nerve terminals. However, a dissociation of the sympatho–adrenal system has been observed in some situations (Young, Rosa and Landsberg, 1984). The increase in plasma noradrenaline concentration in the absence of a concomitant increase in plasma adrenaline concentration seen in the present study may be the result of the relative mildness of the psychological (as well as physical) stress which we imposed on our subjects.

An increase in sympathetic nervous activity can directly stimulate thyroid secretion. We observed no differences in thyroid secretion between the two groups. However, one would not expect to observe an increase in circulating thyroxine as a consequence of such a short period of cooling, since its secretion takes several hours to become manifest.

The catecholamines also have a direct fuel-mobilizing action on liver, muscle and adipose tissue. However, there were no differences in circulating concentrations of lactate or pyruvate between the two groups in the present study. This is perhaps not surprising since, in skeletal muscle at least, adrenaline is more potent in stimulating the β_2-adrenoceptors (Young and Landsberg, 1977) which would increase the production of lactate and pyruvate via glycogenolysis (Day, 1975). In the present study the plasma concentration of adrenaline decreased during cooling.

Plasma glucose concentrations were higher in the MH group compared with the control subjects. This is consistent with an increase in the activity of the sympathetic nervous system. An increase in sympathetic noradrenergic activity would be expected to stimulate the release of glucagon and to suppress the release of insulin from the pancreatic A and B cells, respectively (Frohman and Bernadis, 1971).

Normal healthy individuals vary in their response to thermal stress. To some extent this variation can be explained by body composition and for this reason subjects were matched for body weight, percent body fat and age. The percent body fat did not appear to be associated with the occurrence or absence of shivering as shivering was observed in subjects whose body fat varied from 11.6 to 19.6%, with the overall range being 9.2–21%.

It is possible that the increase in core temperature that occurred immediately after the start of cooling was the result of the combined effects of a decrease in peripheral blood flow and an increase in metabolic heat production. Although the initial redistribution of cool blood from the periphery to the core as a result of peripheral (skin) vasoconstriction might transiently decrease core temperature, this vasoconstriction would be expected subsequently to decrease the thermal conductivity of the subcutaneous tissues. The latter would be expected to reduce heat transfer from the body's core to its shell. In addition, cooling the skin surface would be expected to lead to firing of the peripheral cold receptors, which would stimulate both heat-producing and heat-conserving mechanisms. Since metabolic heat production was increased simultaneously with, presumably, a decrease in peripheral blood flow, the combined effects of these mechanisms might account for the initial increase in core temperature that was observed during cooling.

The differences in heat exchange from the trunk and legs to the suit (as indicated from suit inlet and outlet temperatures) suggest a greater heat loss in the control group. This difference is not associated with any apparent differences in body weight or skinfold thicknesses. It is, therefore, most readily explained by differences in skin perfusion.

The change in heat production was proportional to the change in core temperature during the present study. Thus, the greater the increase in heat production, the less the decrease in temperature. Most of the MH patients had a greater increase in heat production overall and virtually maintained their core temperature. A higher metabolic heat production in the MH group could well be attributable to the augmented sympathetic response in these individuals as indicated by the higher circulating noradrenaline concentration. Both β_1-adrenoceptor-mediated lipolysis and β_2-adrenoceptor-mediated lactate metabolism produce an increase in metabolic heat production (Svedmyr, 1966). Although no differences in circulating lactate concentration were noted in the present study, there may have been a higher turnover rate of plasma FFA in the MH group. This is possible, since noradrenaline does increase FFA turnover in plasma (Steinberg et al., 1964). However, it should be recognized that there are difficulties in interpreting changes in circulating noradrenaline concentration, since these measurements do not necessarily reflect noradrenaline turnover in the sympathetic nerve terminal. Measurements of the rate of noradrenaline turnover are necessary to assess sympathetic activity accurately (Landsberg and Young, 1978; Young, Rosa and Landsberg, 1984).

It is interesting to speculate tentatively that the results of the present study suggest that MH-susceptible individuals may well be able to maintain their deep body temperature more readily under conditions of cold stress than non-susceptible individuals.

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MICROCALORIMETRIC STUDIES IN MALIGNANT HYPERPYREXIA SUSCEPTIBLE INDIVIDUALS

E. RANKLEV, M. MONTI AND R. FLETCHER

SUMMARY

In an attempt to develop a diagnostic test for malignant hyperpyrexia (MH) without the need for open muscle biopsy, we have investigated the change in heat production brought about when platelets and muscle are exposed to halothane and caffeine. Halothane 3% caused platelet aggregation, which was itself associated with heat production. Caffeine 4 mmol litre^{-1} decreased heat production in platelets from both MH susceptible and non-susceptible individuals. Muscle exposed to 4% halothane showed an increase in heat production in both types of tissue. There were no significant differences in heat production between MH-susceptible and non-susceptible tissue in any of the tests.

The only generally accepted method of diagnosing susceptibility to malignant hyperpyrexia (MHS) is *in vitro* testing of muscle (Kalow, Britt and Richter, 1977; Ellis et al., 1978). However, since this is a time-consuming technique which requires an open muscle biopsy, a simpler method of diagnosis would be of value.

Although the primary manifestation of malignant hyperthermia (MH) is an increase in heat production in muscle, platelets also contain contractile elements and have been the focus of attention. Indeed, abnormalities of platelet metabolism and aggregation have been reported (Solomons, Tan and Aldrete, 1978; Zsigmond, Penner and Kothary, 1978) in association with MH.

We have measured *in vitro* the heat produced by exposing small specimens of muscle to halothane and by exposing platelets to halothane and caffeine.

PATIENTS AND METHODS

Muscle preparation

A muscle biopsy was taken from 26 individuals being investigated for susceptibility to MH, and from seven normal controls during other operations. MH-suspected individuals were identified as MH susceptible (MHS), or MH negative (MHN) after the *in vitro* exposure of the muscle to halothane and to caffeine (Ørding, Ranklev and Fletcher, 1984). All muscle biopsies from MH-suspected individuals were from the vastus medialis and included the motor point. The biopsies from the control patients were taken from the rectus abdominis, gluteus maximus or gastrocnemius. Anaesthesia for the biopsies was either femoral nerve blockade or thiopentone–fentanyl–nitrous oxide in oxygen.

After excision the muscle was stored and transported at 4 °C in Krebs–Ringer phosphate (KRP) buffer solution containing glucose 8.25 mmol litre^{-1} and insulin 0.1 iu ml^{-1}. The fibres were dissected to about 1 mm diameter (about 50 mg weight) and placed in the calorimeter within 30 min of excision.

Platelet suspensions

Venous blood samples were collected, from 14 individuals being investigated for MH sensitivity, in 10-ml Vacutainer tubes containing 25 U.S.P. units of sodium heparin (Kabi, Sweden) and 5% Dextran 80 solution 2 ml (Pharmacia, Sweden). Platelet rich plasma (PRP) suspensions were prepared as described by Levin (1971). The concentration of platelets in the cell suspensions was about 150×10^9 litre^{-1}. Duplicate platelet and leucocyte counts were made by phase contrast microscopy. No erythrocytes were observed in the cell suspensions used.

Calorimetric measurements

The studies on muscle were performed in a perfusion calorimeter (Wadsö, 1974) in which the

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fluid was maintained at 37 °C by a heat exchanger to ensure minimal heat loss from the system. Heat production was measured as the change in voltage produced in a thermopile placed round the calorimeter vessel. After 30 min the perfusion fluid was changed to one equilibrated with 4% halothane.

The studies on platelets were performed in microcalorimeters of the thermopile heat conduction type (Spink and Wadsö, 1976). The samples were enclosed in 1.0-ml stainless steel ampoules. Measurements were made under static conditions at 37 °C as described by Monti and Wadsö (1977). Two samples were measured simultaneously. Corrections were made for the heat production of leucocytes in the PRP suspensions (2% of the total heat production (Bandmann, Monti and Wadsö, 1975)) and for the final pH to pH 7.4 (Monti and Wadsö, 1977). The coefficient of variation for the method has previously been determined to be 4% (Monti and Wadsö, 1977).

In the caffeine–platelet study, caffeine diluted in KRP-buffer was added to PRP to a final concentration of 4 mmol litre^{-1}. The control ampoule contained PRP and KRP buffer solution. Samples from nine patients (five MHS and four MHN) were tested. In the halothane–platelet study, platelets were suspended in autologous plasma and the reactant ampoule was equilibrated with 3% halothane for 10 min before measurements were begun. Samples were obtained from one MHS and two MHN patients. In addition, two equivocal patients (MHE (European MH group, 1984)) were tested.

Statistics

Differences were tested by the Mann–Whitney test for unpaired data.

RESULTS

Effect of halothane on heat production in muscle

Figure 1 shows a typical muscle calorimetry tracing. Before the addition of halothane there was a continuous decrease in heat production, possibly reflecting a decrease in the availability of substrate in the cells. The addition of halothane was, in all instances, followed by an increase in the rate of heat production; on many occasions the increase was enough to reverse the trend.

Heat production was measured as the area under the "hump" in the tracing (the shaded area in figure 1). There were no significant differences between MHS ($n = 12$), MHN ($n = 14$) and normal controls ($n = 7$).

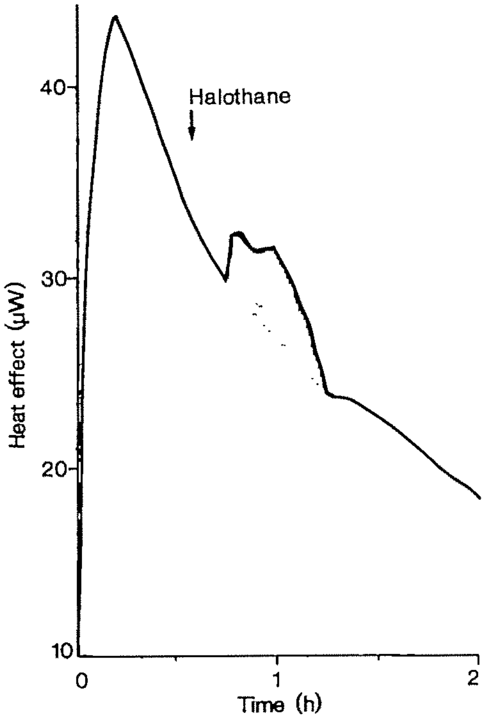

FIG. 1. Microcalorimetry tracing showing effect of halothane on muscle metabolism.

Effect of caffeine on heat production by platelets

Heat production was determined with and without the addition of caffeine to a final concentration of 4 mmol litre^{-1}. In all instances heat production decreased in the suspensions containing caffeine. There were no significant differences between MH-positive and MH-negative patients.

Effect of halothane on heat production by platelets

In four patients (one MHS, two MHN and one MHE) halothane caused an increase in heat production; in one equivocal patient heat production decreased.

DISCUSSION

Measurement of heat production in cells by calorimetry gives information about total cellular metabolic activity. The present method of muscle fibre preparation has been used extensively by other investigators (Lundholm et al., 1975) who were unable to demonstrate morphological or functional alterations in the specimens (Bylund et al., 1976). Muscle for this test was excised and tested at the same time as the muscle used for the *in vitro* halothane and caffeine tests, during which satisfactory viability was demonstrated by repeated electrical stimulation. In the model described above, halothane increased the metabolism of muscle tissue, but there was no significant difference between MHS and MHN individuals. The muscle specimen was not stretched during the test. In the *in vitro* test for MH sensitivity, a halothane contracture cannot usually be demonstrated at zero tension. It may, therefore, be necessary to stretch the muscle to 1–2 g tension in order to observe a difference between MHS and MHN individuals.

Halothane had a variable effect on heat production by platelets, increasing it in four patients and decreasing it in one. Although the MHS patient showed the greatest increase in heat production, the differences were too small to be of any diagnostic value. More importantly, halothane has a tendency to make platelets aggregate. Because aggregation *per se* causes an increase in heat production by platelets (Ross, Fletcher and Jamieson, 1973) we do not believe that this method can have any diagnostic value.

Caffeine, on the other hand, decreased heat production in both MHS and MHN platelets, although the effect of caffeine on the intact organism is to increase heat production (Acheson et al., 1980). Other xanthine derivatives have been shown to have the same effect on platelets (Monti and colleagues, in preparation).

We conclude that the microcalorimetric methods described above cannot be used to distinguish between tissues from MHS and MHN individuals.

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DILTIAZEM INHIBITS HALOTHANE-INDUCED CONTRACTIONS IN MALIGNANT HYPERTHERMIA-SUSCEPTIBLE MUSCLES *IN VITRO*

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SUMMARY

The ability of diltiazem to suppress halothane and halothane–caffeine induced contractures in malignant hyperthermia (MH) susceptible pig muscle, was tested in vitro. *Muscle specimens were divided into two groups and tested with a modified halothane–caffeine contracture test. One group acted as the control; the other group was pretreated with diltiazem 20 µmol litre^{-1}. The control muscles developed contractures attributable to halothane and halothane–caffeine, whereas the diltiazem-treated specimens did not. Increases in muscle twitch tension as a result of halothane or halothane–caffeine exposure occurred in treated and untreated specimens, but were significantly delayed in the presence of diltiazem. Muscle exhaustion observed after halothane and halothane–caffeine exposure in the control specimens did not occur in the diltiazem treated muscles.*

Malignant hyperthermia (MH) is a rare, but serious, complication of anaesthesia with a high mortality rate. During the syndrome, transmembranous and intracellular movements of Ca^{2+} — caused by genetically transmitted defects in calcium ion regulation — lead to pathological muscle contracture, increased energy consumption, and muscle cell death (Williams, 1976; Gronert, 1980). Dantrolene, which may block the intracellular movement of Ca^{2+} (Britt, 1984), is currently the drug of choice in the treatment of the syndrome (Nelson and Flewellen, 1983; Britt, 1984). Since muscle contracture in MH is dependent on an increase in the intracellular concentrations of unbound Ca^{2+} (Britt et al., 1982), blockade of transmembranous Ca^{2+} influx by calcium entry blockers was suggested as a possible mode of treatment (Bikhazi, Thomas and Foldes, 1979). A single observation in isolated human MH susceptible muscle showed that diltiazem was able to suppress halothane and halothane–caffeine induced muscle contracture (Iwatsuki, Koga and Amaha, 1983).

The purpose of this investigation was to assess, in a controlled study, the suppressive effect of diltiazem on halothane- and halothane–caffeine-induced contracture of MH susceptible pig muscle.

MATERIALS AND METHODS

Muscle specimens (biceps femoris) were taken from 10 MH-susceptible, inbred Poland China Pigs, and two normal control pigs (susceptibility tested at 8–10 weeks of age; halothane inhalation test) (Williams, 1976). The specimens were excised under thiopentone–oxygen–nitrous oxide anaesthesia, immediately cut into 3 × 2 × 40-mm strips and placed in a constant temperature (37 °C) organ bath containing 100 ml of modified Krebs Ringer solution (Bikhazi, Thomas and Foldes, 1979) containing calcium 1.4 mmol litre^{-1}; magnesium 1.2 mmol litre^{-1}; potassium 5.9 mmol litre^{-1}; phosphorus 1.2 mmol litre^{-1}; chloride 122.7 mmol litre^{-1}; and aerated with 5% carbon dioxide in oxygen. After 60 min of equilibration the muscle was stimulated directly with supramaximal rectangular impulses (1 ms, 0.2 Hz) (Techtronics). Isometric contractions were measured by force displacement transducers (Grass FT03) and recorded continuously (HP7758). Pretension was adjusted until the

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amplitude of muscle twitches could not be increased further (average 3 g).

After a steady state of baseline and muscle twitch tension had been established 4% halothane was added to the aeration of the organ bath for 20 min. The muscle strips were then allowed to return to a second steady state of baseline and twitch tension, The strips were again exposed to 4% halothane for 20 min and then caffeine 0.3 mmol litre^{-1} was added to the organ bath. A second muscle strip of the same specimen was treated with the same procedure except that diltiazem 20 µmol litre^{-1} was added to the organ bath 20 min before the administration of the halothane. Baseline shifts caused by halothane alone or by halothane–caffeine of more than 10% of control twitch tension were defined as being MH-positive. This modification of the generally accepted *in vitro* test (Gronert, 1979) was used to find a better relationship between muscle specimens of different strengths. The amplitude of twitch tension and the time until maximum twitch amplitude under the influence of halothane and halothane–caffeine, respectively, were determined. The differences between the control and the diltiazem-pretreated muscle strips were evaluated for statistical significance by using the Wilcoxon rank sum test and Fisher exact test. The level of significance was taken to be $P < 0.05$.

RESULTS

Mean and standard errors of the mean of the maximum increase in muscle twitches (% of control), time to maximum twitch (min), and number of muscles which showed an increase in baseline tension caused by halothane or halothane–caffeine are shown in table I. There were no significant differences in the percentage of maximum twitch increases between the pretreated and unpretreated muscles. However, the maximum twitch tension developed significantly later in the diltiazem-pretreated group. Increases in baseline tension which developed in the unpretreated muscle strips could be suppressed by diltiazem. After exposure to halothane, the unpretreated muscle strips developed a steady state of twitch tension 26.9 ± 5.9% less than the control values. The diltiazem-pretreated specimens re-established a steady state of twitch tension which was equal to the control values.

TABLE I. *Characteristics of diltiazem pretreatment (mean ± SEM).* N = *Number of events.* $^{*}P < 0.05$

	Control ($n = 10$)	Diltiazem ($n = 10$)
4% Halothane		
Twitch increase (%)	37.9±13.1	38.9±6.5
Time to max. twitch (min)	6.9±0.8*	12.5±1.2*
Baseline shift (*N*)	10*	0*
4% Halothane + caffeine		
Twitch increase (%)	19.2±12.9	36.7±13.0
Time to max. twitch (min)	2.3±0.3*	6.9±0.9*
Baseline shift (*N*)	10*	2*

Diltiazem initially decreased the control twitch tension, delayed the increase to maximum twitch tension with halothane, suppressed the elevation in baseline, and allowed re-establishment of the control twitch tension after exposure to halothane. However, in two of the preparations, diltiazem failed to suppress the halothane–caffeine-induced contractions (fig. 1).

The muscle strips taken from the two normal pigs showed no elevations in baseline during halothane or halothane–caffeine exposure with or without diltiazem pretreatment. However, the increase in time required to develop maximum twitch amplitude after diltiazem pretreatment was similar in the MH and the normal pig muscle.

DISCUSSION

The Ca^{2+}-entry blocker diltiazem suppressed halothane- and halothane–caffeine-induced contracture of MH susceptible muscle *in vitro*. This confirmed a single observation made in isolated human MH susceptible muscle (Iwatsuki, Koga and Amaha, 1983). Ca^{2+}-entry blockers have been shown to protect hypoxic myocardial muscle by interference with excitation–contraction coupling and suppression of an uncoupling of the oxidative phosphorylation, thereby conserving energy reserves (Watts, Koch and La Noue, 1980; Matlib et al., 1983; Hoff, 1984). The delay in the increase to maximum twitch tension and the re-establishment of control twitch tension after halothane exposure in the diltiazem-pretreated specimens would suggest similar effects in the MH-susceptible muscle. The ability to suppress contracture in MH-susceptible pig muscle induced by standard MH trigger-substances, and the well known cardiovascular effects of diltiazem and Ca^{2+}-entry blockers in general represent drug properties which should be useful in the treatment of the clinical manifestations of MH. Williams and colleagues (1985) have used diltiazem

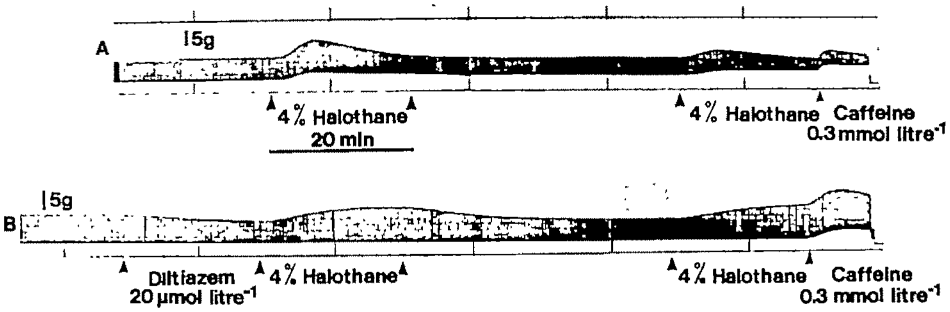

FIG. 1. Control (A): typical MH contracture during 4% halothane for 20 min and 4% halothane for 20 min plus caffeine 0.3 mmol litre^{-1}. Notice the decay in twitch force after halothane and halothane–caffeine respectively. Diltiazem pretreatment (B) 20 min before halothane exposure decreased muscle twitch tension, prevented contracture, and delayed increase in twitch amplitude caused by halothane. Notice the lack of decay in twitch force after halothane exposure as a result of diltiazem pretreatment. This strip shows contracture response to combined halothane–caffeine stress as happened in two out of 10 muscle strips in spite of diltiazem pretreatment.

3.4–8.9 mg kg^{-1} alone in the successful treatment of MH in five MH-susceptible pigs. Subsequent complete heart block in two pigs required adrenaline and calcium chloride to restore cardiac function.

Diltiazem may be more effective therapeutically for MH than verapamil (Zukaitis et al., 1982, 1983) in the treatment of porcine MH.

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DERMAL EFFECTS OF COMPOSITIONS BASED ON THE EUTECTIC MIXTURE OF LIGNOCAINE AND PRILOCAINE (EMLA)

Studies in Volunteers

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SUMMARY

The effects of the cutaneous application of EMLA cream (a eutectic mixture of lignocaine and prilocaine in their base form) were studied in volunteers. When tested by pin-prick, EMLA cream 2.5% and 5% produced analgesia of the area tested, the cream being most effective if left in contact with the skin for 60 min. The pain produced by the insertion of an i.v. cannula was successfully blocked by the application of this formulation, especially if applied to the antecubital area. Temporary blanching of the skin areas was frequently observed on removal of the occlusive tape bandages, but prolonged, or repeated, application of 5% EMLA cream did not produce local skin reactions. Tests for delayed hypersensitivity reactions were negative. Plasma concentrations of lignocaine and prilocaine were low after a standard application.

Although it is the cationic form of a local anaesthetic agent which blocks the transmission of impulses within the nerve (Covino and Vassallo, 1976), it is the uncharged (base) form which penetrates and diffuses into the tissues after topical or parenteral administration. Effective tissue penetration can be achieved after topical application as follows:

(1) *Water soluble salt in water.* In an aqueous solution of the hydrochloride salt of an amino-amide local anaesthetic, the concentration of the uncharged form depends on the pK_a, which means that only a portion of the local anaesthetic is in the form suitable for tissue penetration. Consequently, to be effective on topical application, the local anaesthetic must be used in high concentration, with the attendent risk of toxic complications. On the other hand, the presence of water in such formulations increases the likelihood of penetration through the skin (Monash, 1957).

(2) *Base in alcoholic solvent.* Since local anaesthetic bases are freely soluble in various alcoholic solvents, it is possible to obtain a high concentration of the base by dissolving it in, for example, ethyl alcohol, as in local anaesthetic sprays or ointments. As such compositions do not contain water, which would precipitate the local anaesthetic, they have poor penetrative properties if applied to the intact skin. They are, however, active on application to mucous membranes (Dalili and Adriani, 1971; Adriani and Dalili, 1971).

(3) *Oil-in-water emulsion.* Recent pharmaceutical research has shown that it is possible to combine a high concentration of the local anaesthetic base with a high water content by using oil-in-water emulsions (Broberg and Evers, 1981; Brodin et al., 1984), thus achieving an increased uptake of local anaesthetic via the intact skin (by including water in compositions containing the base). This seemingly paradoxical effect is achieved because the emulsion droplets contain the local anaesthetic base in high concentration (e.g. 20% lignocaine) while the total concentration in the emulsion is low (only 5% lignocaine).

A further increase in analgesic efficacy has been demonstrated with oil-in-water emulsions, based on the eutectic mixture of lignocaine and prilocaine (Broberg and Evers, 1981). Brodin and colleagues (1984) reported that a mixture of lignocaine and prilocaine in base form had a melting point considerably lower than that of each ingredient. This means that two crystalline powders interact in such a way that, when mixed with each other,

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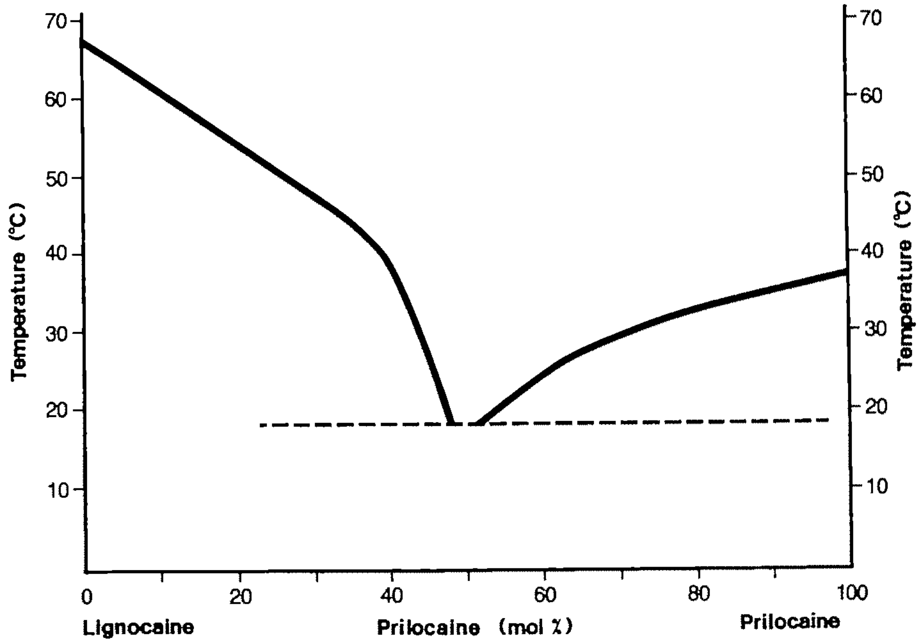

FIG. 1. Phase diagram of the lignocaine/prilocaine system. At around prilocaine 50 mol% mixed with lignocaine, the system is liquid at 18 °C. At lower and higher prilocaine and lignocaine concentrations, the mixture is solid in crystalline form. (Modified from Brodin et al., 1984.)

a liquid is formed at approximately room temperature (fig. 1). This is of significance in the preparation of oil-in-water emulsions as it obviates the need for dissolving the local anaesthetic base in an oil before the addition of the emulsifier. By this method it is possible to increase further the concentration of local anaesthetic in the emulsion droplets from approximately 20% (lignocaine) to about 80% (lignocaine–prilocaine) in eutectic formulations, while still keeping the total concentration of local anaesthetic low (5%).

Although it has been possible to use several different local anaesthetics, or combinations of more than two substances, to make eutectic mixtures (Broberg and Evers, 1981), the choice of lignocaine and prilocaine was obvious for many reasons, particularly in regard to their known margins of safety. The oil-in-water emulsions in our studies were based upon a 50:50 eutectic mixture of lignocaine and prilocaine bases in combination with a conventional and documented emulsifier, Arlatone, and water.

The aim of the present investigation was to study the dermal analgesia produced by the application, to the skin, of compositions based upon the eutectic mixture of lignocaine and prilocaine, and to study the local effects on the skin after prolonged and repeated application. In addition, evidence of delayed hypersensitivity reactions was sought. Plasma concentrations of lignocaine and prilocaine were measured following a standard application.

SUBJECTS, MATERIALS AND METHODS

Volunteers, between 20 and 40 yr and of either sex, were medically examined before the investigation. A full medical history was obtained and a complete blood analysis was carried out. Any volunteer with a previous reaction to any local anaesthetic was excluded. A double-blind technique with placebo control was used in all the series. Active or placebo formulations were applied to the different test areas according to predetermined randomized patterns.

Dermal analgesia

(1) *Influence of concentration and duration of application on dermal analgesia.* The test compositions of this series consisted of 1.0%, 2.5% and 5% EMLA emulsions and placebo.

Porous cellulose-fibre pads (2 × 3 cm) soaked with the different formulations were applied on the volar side on both arms. Occlusive tape bandages

(Blenderm (3M)) were applied to cover the pads. The bandages were removed after 30 min on one arm, and after 60 min on the other arm. Dermal analgesia was tested with a modified pin-prick technique, using the relatively blunt reverse side of a disposable 27-gauge sterile dental needle (Monoject, Sherwood). Each needle was used on one test occasion and then discarded. Each skin test area was pin-pricked 10 times, the needle pricks covering the whole test area. This test was carried out immediately after removal of the bandage, and at 30-min intervals for up to 240 min. A score index was obtained from the volunteer, by noting the number of painfree pin-pricks out of the 10 in each area. The volunteers were fully instructed before each study on how to differentiate between the perception of touch and that of sharp pain. During the investigation each volunteer's ability to discriminate between these two types of perception was assessed by pin-pricking outside the treated skin areas also. All pin-prick studies were carried out by the same investigator (H.E.).

(2) *Influence of viscosity on dermal analgesia.* The technique used in this series was identical to that used in the first series, with one exception: instead of pin-pricking the whole test area at each 30-min test, the test skin area was divided in six equal areas, each of which was pin-pricked on each test occasion. In this way a fresh test area was pin-pricked each time, minimizing the local circulatory effects produced by the needle. Using 2.5 % and 5 % EMLA compositions, the viscosity was modified using Carbopol in three different concentrations. This provided three different viscosities in the test formulations: an emulsion (no viscosity increasing agent), a lotion and a cream formulation. A 5 % lignocaine ointment (Xylocaine 5 % ointment, Astra) and a placebo were included in the series for comparison. Application time was 60 min.

(3) *Test of dermal analgesia by skin penetration and intravascular placement of i.v. needles.* After application of 5 % EMLA or placebo, and following the use of an occlusive dressing for 60 min, the pain on needle insertion through the skin, and the subsequent intravascular placement of standard i.v. needles (Venflon 140, 17 gauge, 1.4 mm o.d., 45 mm b.s. Luer-lock) was assessed.

The skin areas studied were the dorsum of the hand, the lower arm area and the antecubital fossa. The pain experienced by the volunteers was recorded when inserting the needle, immediately after removal of the occlusive bandages and after intravascular placement of the needle. The second procedure, moving the needle to an intravascular position after insertion, was made after the initial pain of skin penetration had receded completely. The pain produced by the two procedures was classified as no pain (= 0), slight pain (= 1) and painful (= 2).

Tolerance studies

(4) *Prolonged application.* EMLA 5.0 % cream or placebo were applied under occlusive tape bandages on the skin of the back. Application time was 24 h. Signs of local irritation were recorded immediately after removal of the bandages as: − = no reaction, + = erythema, + + = erythema and papules, + + + = vesicles.

(5) *Repeated application to the same area of skin.* EMLA 5.0 % cream or placebo cream was applied on marked areas of the skin on the volar surface of the arms. The same areas were treated with one, two and three applications (60 min) with 24-h intervals. Recording of signs of local irritation was made on three different occasions, immediately on removal of the bandages. The scale used by the recording of local effects was the same as that used in the second series of investigations.

Signs of local irritation were recorded after one, two and three applications.

(6) *Test of delayed hypersensitivity reaction.* EMLA 5.0 % cream, EMLA 2.5 % cream, 5.0 % lignocaine cream or placebo cream were applied in a standard epicutaneous skin test procedure (AL-test, Imeco), on the skin of the back. Application time was 48 h and the skin reactions were observed 50 h after application.

All volunteers taking part in the study of delayed hypersensitivity had been previously exposed to EMLA cream on several occasions, in other series of investigations.

Pharmacokinetic studies

(7) *Percutaneous absorption of lignocaine and prilocaine.* EMLA 5 % cream was applied to the skin on the lateral side of one thigh with an application time of 60 min. To ensure a standard area of application, a plastic frame with a central opening of 300 cm^2 was applied to the skin of the thigh, enabling a thick layer of the cream to cover an identical area in all subjects. In each volunteer, 20 g of the cream, containing 500 mg of each local anaesthetic, was used. After 60 min application, the occlusive bandage was removed and pin-

pricking of the test areas was carried out every 30 min for up to 240 min using the same technique as in the previous series. Blood samples were drawn from an antecubital vein at 30, 60, 90, 120, 180 and 240 min after the application of the bandage. Plasma concentrations of lignocaine and prilocaine were analysed by mass fragmentography, carried out at the Department of Analytical Chemistry, Astra Läkemedel AB, Södertälje, Sweden.

(8) *Influence of preperative skin cleaning on plasma concentrations of lignocaine and prilocaine.* The application procedures and amounts of 5% EMLA cream used were identical to those used in the previous series, as were the assessment by pin-prick and the blood sampling procedure. Immediately after removal of the occlusive bandage, the application site was cleansed for 2 min by a qualified nurse, who simulated the procedure of regular preoperative cleaning. The disinfectant used contained 0.5% chlorhexidine digluconate in 70% alcohol.

RESULTS

Dermal analgesia

(1) *Influence of concentration and duration of application on dermal analgesia.* EMLA 2.5% and

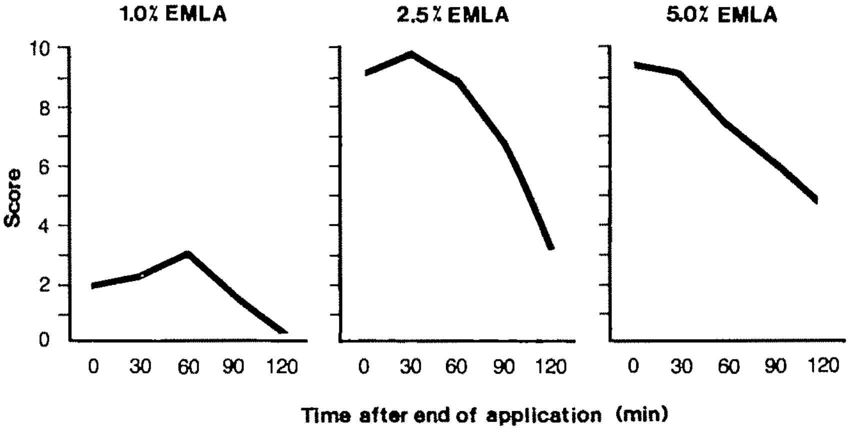

FIG. 2. Influence of concentration on dermal analgesia. Mean painfree scores at different times of observation, after 60 min applications of 1.0%, 2.5% and 5.0% EMLA emulsions. Number of volunteers = 12.

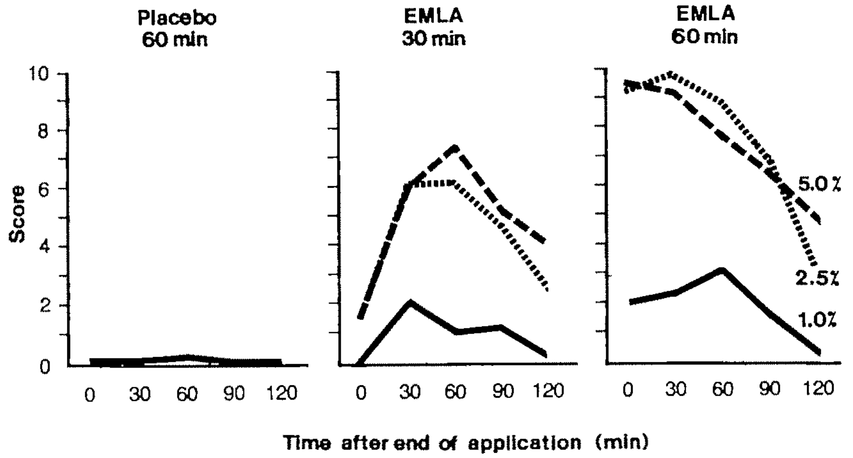

FIG. 3. Influence of duration of application on dermal analgesia. Mean painfree scores at different times of observation after 30- and 60-min applications of 1.0% 2.5% and 5.0% EMLA emulsions or placebo. Number of volunteers = 12.

5.0% emulsions were effective in producing analgesia of the skin, while the lower concentrations and the placebo were significantly less effective (fig. 2).

On removal of the occlusive bandage after 30 min application, the dermal analgesia was poor with all formulations. When tested 30 min later, however, dermal analgesia had improved significantly. After 60 min application, both the 2.5% and the 5% EMLA emulsions were found to be highly effective in blocking the pain of pin-prick (fig. 3).

(2) *Influence of viscosity on dermal analgesia.* Dermal analgesia was not influenced by the addition of the two tested concentrations of Carbopol, a viscosity increasing agent (fig. 4).

(3) *Test of dermal analgesia by skin penetration and intravascular placement of i.v. needles.* The pain felt by the volunteers on the insertion of the needle through the skin and on intravascular placement was blocked to a significantly greater extent by 5% EMLA than by placebo in the antecubital area and on the dorsum of the hand. The differences between the two formulations were insignificant when applied on the lower arm area (fig. 5). If applied in the antecubital area, 5% EMLA cream was completely effective in blocking the pain of needle insertion in all volunteers.

Tolerance studies

(4) *Prolonged application.* None of the applied formulations, 2.5% EMLA, 5.0% EMLA or placebo, caused any signs of local irritation in any of the volunteers, with the exception of two areas in which very slight redness was observed after removal of the bandage covering the 2.5% EMLA formulation. Outside these two areas there was some irritation from the tape bandage.

(5) *Repeated application.* The repeated application of either the 5% EMLA cream or the placebo cream did not cause any signs of local irritation in any of the subjects.

(6) *Test of delayed hypersensitivity reaction.* No delayed skin reactions were observed on any of the areas to which 2.5% EMLA, 5% EMLA or placebo was applied.

Pharmacokinetic studies

(7) *Percutaneous absorption of lignocaine and prilocaine.* After removal of the occlusive dressing, applied to the lateral side of the thigh and covering 300 cm^2 of the skin area for 60 min, the blood concentrations of lignocaine and prilocaine were found to be low (fig. 6). However, the variation between subjects in the concentration of both substances was high (table I).

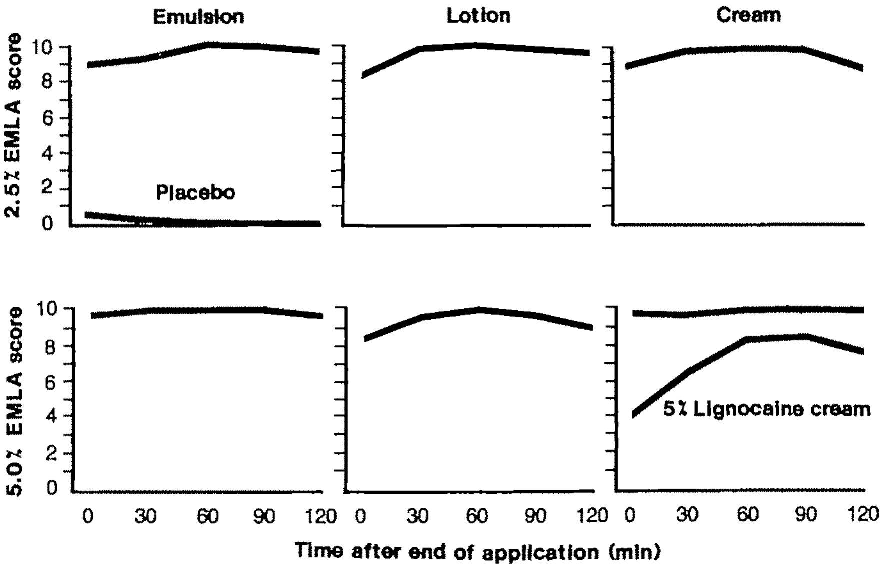

FIG. 4. Influence of viscosity on dermal analgesia. Mean painfree scores at different times of observations after 60-min applications of 2.5% and 5.0% EMLA emulsion, lotion and cream, 5.0% lignocaine cream or placebo. Number of volunteers = 12.

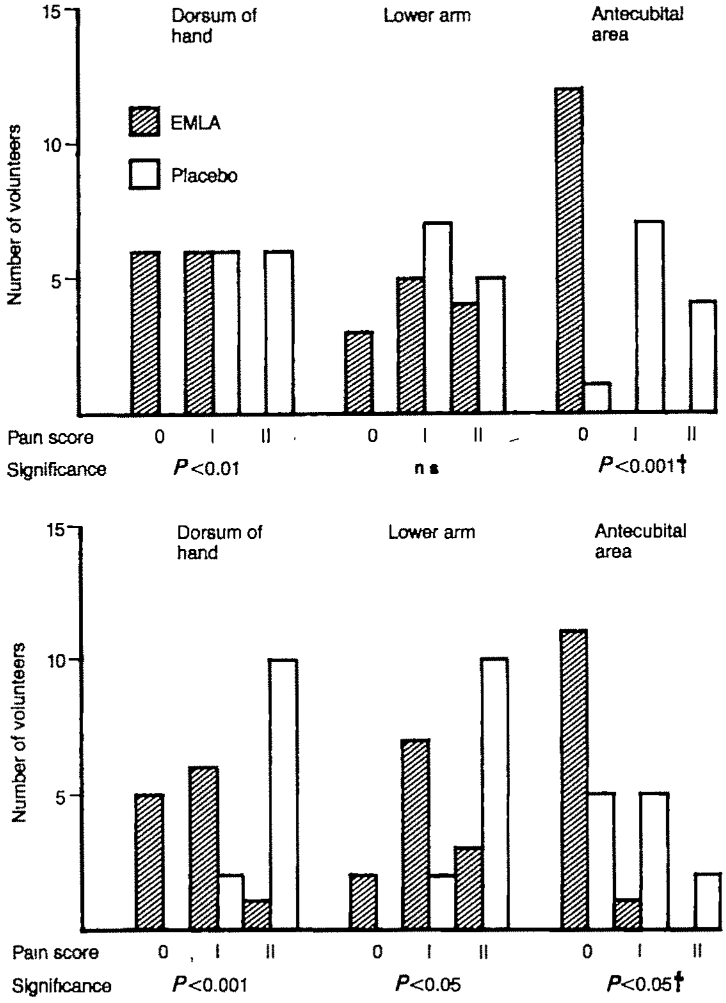

FIG. 5. Pain scores on insertion of i.v. needle: top = skin penetration; bottom = vessel wall penetration. Number of volunteers = 12. †McNemar test.

TABLE I. *Mean anaesthetic concentrations (ng/ml plasma), all volunteers. Statistical comparison was by paired* t *test*

	Time after application (min)					
	30 ($n = 20$)	60 ($n = 20$)	90 ($n = 20$)	120 ($n = 20$)	180 ($n = 19$)	240 ($n = 20$)
Lignocaine						
(ng ml^{-1})	8.2	24.0	24.0	68.4	74.5	65.4
SD	7.02	27.68	27.68	47.95	35.26	25.12
Prilocaine						
(ng ml^{-1})	1.2	3.6	13.4	21.4	24.7	19.9
SD	3.83	7.87	17.00	19.35	14.93	12.19
Lignocaine/ prilocaine						
t	3.91	3.17	1.46	4.07	5.67	7.29
P	< 0.001	<0.01	ns	< 01.001	< 0.001	<0.001

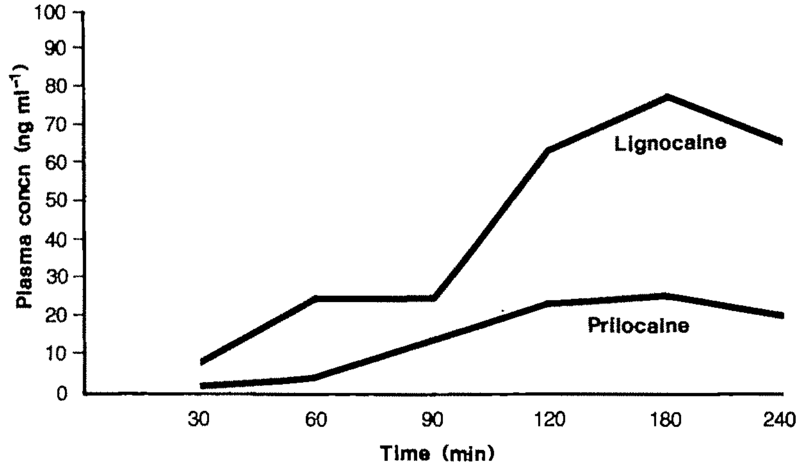

FIG. 6. Mean plasma concentrations of lignocaine and prilocaine. Different times of observation after a 60-min application of 5.0 % EMLA cream on a 300-cm^2 skin area on the lateral side of the thigh. Number of volunteers = 20.

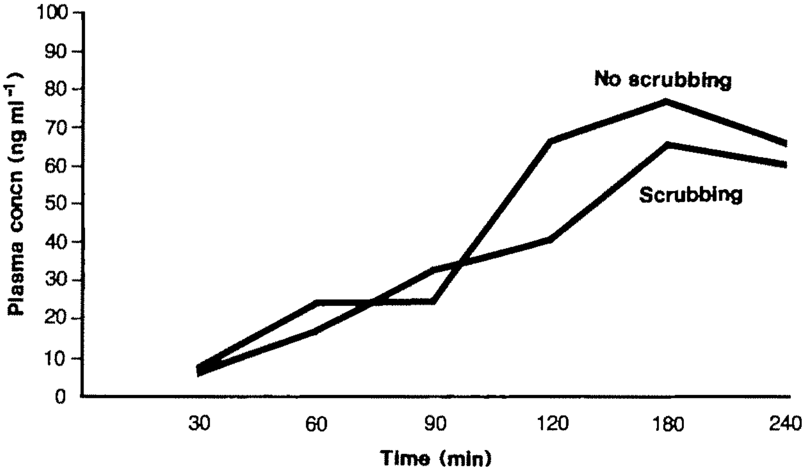

FIG. 7. Mean plasma concentrations of lignocaine. Different times of observation after a 60-min application of 5.0 % EMLA cream on a 300-cm^2 skin area on the lateral side of the thigh, with and without preoperative cleansing of the skin. Number of volunteers = 20.

(8) *Influence of preoperative cleaning upon lignocaine and prilocaine concentrations.* The cleansing procedure immediately after removal of the occlusive bandage decreased the concentrations of lignocaine in the blood samples compared with the values found in the previous series, where no cleansing had been carried out (fig. 7). The prilocaine concentrations were not influenced by the cleansing procedure (fig. 8). As in the previous series, the variation in serum concentrations between subjects was substantial (table II).

DISCUSSION

New formulations based on the eutectic mixture of two, widely used, local anaesthetic substances, lignocaine and prilocaine (in their base form) have been investigated.

The pin-prick studies demonstrated clearly that concentrations lower than 2.5 % of lignocaine/prilocaine were significantly less active in producing dermal analgesia than the 2.5 % and 5.0 % preparations. In addition, it was noted that an

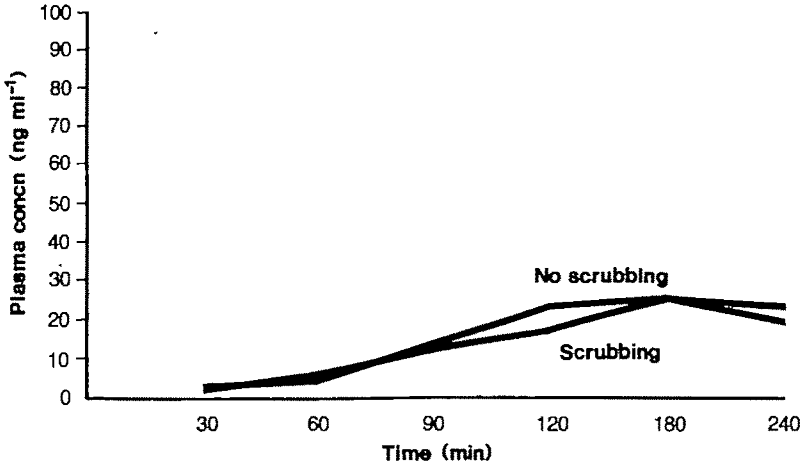

FIG. 8. Mean plasma concentrations of prilocaine. Different times of observation after a 60-min application of 5.0 % EMLA cream on a 300-cm² skin area on the lateral side of the thigh, with and without preoperative cleansing of the skin. Number of volunteers = 20.

TABLE II. *Mean anaesthetic concentrations (ng/ml plasma), all volunteers, after the cleansing procedure*

	Time after application (min)					
	30 (n = 20)	60 (n = 20)	90 (n = 20)	120 (n = 20)	180 (n = 20)	240 (n = 20)
Lignocaine						
(ng ml⁻¹)	6.3	18.2	31.9	40.8	66.0	59.5
SD	9.82	24.86	29.20	30.87	34.32	28.90
SEM	2.1958	5.5589	6.5293	6.9027	7.6742	6.4622
Prilocaine						
(ng ml⁻¹)	1.0	4.4	12.5	17.5	24.6	22.0
SD	2.58	11.65	15.80	15.18	13.40	11.03
SEM	0.5769	2.6050	3.5330	3.3944	2.9963	2.4664

application time of 60 min under an occlusive dressing was desirable to achieve a high frequency of painless pin-pricks. An application time of 30 min produced limited analgesia, although, when tested 30 min later, the analgesia scores had increased to values similar to those after 60 min application time. A preparation with a higher viscosity than that of the emulsion can be of clinical interest from a practical point-of-view; for example, ease of application. In our studies it was found that the production of dermal analgesia to pin-prick was not altered by the addition of a viscosity increasing agent. In those series of experiments where the pin-pricks had been distributed evenly over the whole test area, the duration of dermal analgesia was comparatively short. When the pin-prick testing was modified, and a fresh area was used at each test, the duration of analgesia was found to be much longer. This may have clinical consequences, since any disturbance of the local circulation, by scratching or rubbing, may decrease the duration of dermal analgesia.

In the series in which the pain induced by the introduction of an i.v. needle and its subsequent placement in a vein was investigated, the difference between the active formulation and placebo was insignificant in the lower arm area. In the two other areas studied (the antecubital vein and the dorsum of the hand) the difference was significant in favour of the 5% EMLA cream. It is interesting to observe that these differences were also observed as the needle penetrated the vessel wall, at a distance of about 10 mm from the point of skin puncture.

Skin reactions to the clinical use of 5% EMLA, applied to intact skin, are unlikely. The temporary pallor of the skin treated with 5% EMLA cream seems to be caused by constriction of the peripheral capillary bed although the precise mechanism is unknown at present. In pilot studies, using a conventional skin temperature probe, the temperature of the skin in the areas showing a blanching effect was not found to be lower than that of the untreated skin areas outside the site of application. Investigations aimed at finding an explanation of this phenomenon are under way at present.

When 5% EMLA cream 20 ml was applied to the lateral surface of the thigh for 60 min, the plasma concentrations in blood sampled from an antecubital vein were found to be significantly lower than those considered likely to cause toxic effects. The prilocaine concentrations were found to be lower than those of lignocaine and so accord with previously investigated distribution properties of the two agents (Scott et al., 1972).

It was interesting to find that the concentrations of lignocaine were decreased more after the pre-operative cleansing procedure than the prilocaine concentrations, when one considers that identical amounts of both agents were applied. The phenomenon is difficult to explain as both local anaesthetics are freely soluble in ethyl alcohol.

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COMPARISON OF THE VASOACTIVITY OF AMIDE AND ESTER LOCAL ANAESTHETICS

An Intradermal Study

D. G. WILLATTS AND F. REYNOLDS

SUMMARY

The vascular effects and duration of action of two ester-linked local anaesthetics, procaine and amethocaine, and four amide-linked local anaesthetics, cinchocaine, lignocaine, mepivacaine and prilocaine, were investigated in 10 volunteers by intradermal injection using a double-blind technique. Procaine and amethocaine produced marked vasodilatation; weal formation was observed at 80% of the amethocaine injection sites. Mepivacaine had a marked vasoconstrictor effect; the other three agents produced more variable vasoactivity. Duration of action was concentration-dependent for all six drugs, the slopes of the log dose–duration plots reflecting the observed vasoactivity.

The intrinsic vasoactivity of a local anaesthetic agent is one of the factors determining its rate of removal from the site of action. Lignocaine, and other amide local anaesthetics, have been shown to possess vasoconstrictor properties, especially at low concentrations (Aps and Reynolds, 1976; Reynolds, Bryson and Nicholas, 1976). Cocaine, an ester-linked agent, produces marked vasoconstriction by inhibition of noradrenaline uptake (Iversen, 1965), although alternative mechanisms such as the mobilization of Ca^{2+} (Daniel and Wolowyk, 1965) and the release of endogenous catecholamines (Vohra, 1970) may contribute to cocaine-induced smooth muscle contraction in other tissues. The intrinsic vasoactivity of other ester-linked anaesthetics, such as procaine and amethocaine, is less reliably documented.

The intradermal method of measuring local anaesthesia and vasoactivity gives results which are consistent with other methods (Åberg, 1972; Luduena, Bogado and Tullar, 1972; Aps and Reynolds, 1978; Fairley and Reynolds, 1981). Previous intradermal studies in human volunteers (Aps and Reynolds, 1976; Fairley and Reynolds, 1981) have demonstrated the direct action of amide local anaesthetics on cutaneous blood vessels and the effect this may have on the relationship between concentration and duration of action. The present study was designed to compare the vasoactivity, at various concentrations, of two ester-linked local anaesthetics with that of four amide-linked agents, using the intradermal route.

SUBJECTS, MATERIALS AND METHODS

Solutions

Each of the six local anaesthetics was prepared as an aqueous solution of the hydrochloride salt, containing 0.1% sodium metabisulphite (to stabilize the esters) and sufficient sodium chloride to render it isosmotic with physiological saline. Ampoules of the solutions were randomly coded and sterilized by autoclaving. The following solutions were administered:

Procaine hydrochloride	0.1%	0.3%	1.0%
Amethocaine HCl	0.025%	0.0833%	0.25%
Cinchocaine HCl	0.01%	0.033%	0.1%
Lignocaine HCl	0.1%	0.33%	1.0%
Racemic mepivacaine HCl	0.1%	0.33%	1.0%
Racemic prilocaine HCl	0.1%	0.33%	1.0%
Sodium chloride	0.9%	("control solution")	

Subjects

The subjects were 10 fit adults (eight male) whose ages ranged from 21 to 40 years. One subject was an author (D.G.W.); the others were medical students or medical and laboratory colleages. All gave informed consent.

Procedure

The study was carried out in two parts. In the first, amethocaine, lignocaine and prilocaine (each

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at three concentrations) and physiological saline (control solution) were tested in each of the 10 subjects. In the second part, procaine, cinchocaine and mepivacaine each in three concentrations, and saline were tested on the same 10 subjects. The solutions were injected intradermally on the flexor surface of both forearms; each subject received a pair of 0.1-ml injections of each of the 10 solutions, spaced at 40-mm intervals. The position of each solution varied randomly between the subjects and was known to neither subject nor investigator. The appearance of each bleb was noted 5–10 min after injection, by which time the initial distension had disappeared. Colour changes were classified as pink, nil or pale. Any haemorrhagic changes were recorded.

Ten minutes after injection, every 5 min for the first 1 h and subsequently every 10 min until complete recovery, analgesia was assessed by pricking the central area of each bleb with a lancet 5 times while the subject looked away. For each solution, the number of times out of 10 that the prick felt sharp was recorded; the time of 50% recovery was taken as the time at which the sharpness score reached 5 out of 10. If this occurred between two time intervals, the mid-point of the interval was taken. If the initial score at 10 min was 6, 7 or 8, the 50% recovery time was recorded as 5 min; with an initial score of 9 or 10, 50% recovery time was taken to be zero. The results for the control solution from the two parts of the study were combined.

Differences in proportions were analysed using the Chi-squared test with Yates' correction. The GLIM3 linear modelling computer program (Baker and Nelder, 1978) was used to calculate the slopes of the linear regression lines of log concentration *v*. duration of action for each drug in each subject; the significance of the differences between the mean slopes for each drug was evaluated by a one-way analysis of variance, with logarithmic transformation of the slopes to decrease differences in their standard deviations. A value of P less than 0.05 was considered statistically significant.

RESULTS

Vascular effects

All local colour changes were transient and no permanent tissue damage occurred. Only two haemorrhagic changes were observed, one with 1.0% lignocaine, the other with 0.1% prilocaine.

The vasoactivity of the six agents, expressed as

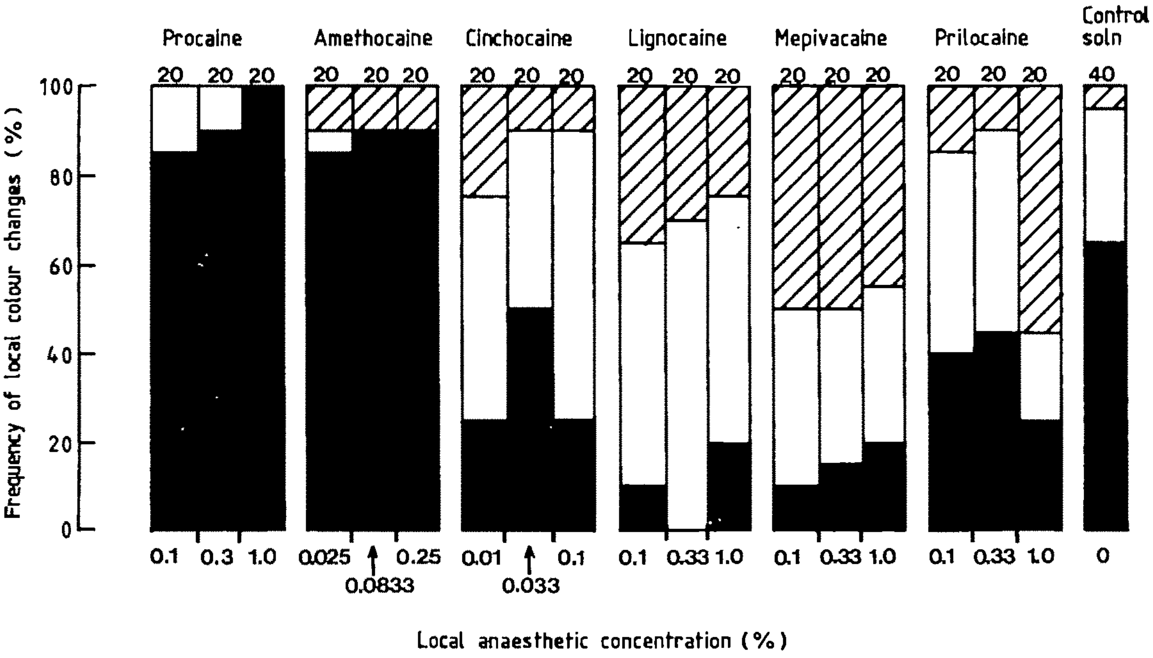

FIG. 1. Percentage frequency of local colour changes. ■ = Pink; □ = nil; ▨ = pale. The numbers above the columns indicate the total numbers of injections of each solution,

percentage frequency of local colour changes at different concentrations, is shown in figure 1. Procaine and amethocaine both showed vasodilator activity, which was significantly greater than that produced by saline ($P < 0.05$), at both intermediate and highest concentrations. No vasoconstriction occurred with procaine at any concentration; that shown by amethocaine was not concentration-dependent and did not differ significantly from the effects of the saline.

There was a marked difference in appearance between the procaine and amethocaine injection sites. In all instances where procaine produced vasodilatation, the area of redness was well demarcated and showed no local oedema. In contrast, the vasodilatation produced by amethocaine extended over a larger area with irregular margins — a typical "flare" response; in addition, weal formation occurred at 12 injection sites at the lowest amethocaine concentration, 16 at the intermediate and 16 at the highest concentration.

The four amide local anaesthetics all produced less vasodilatation at all concentrations than did saline. All three concentrations of lignocaine and mepivacaine produced vasoconstriction significantly more frequently than saline ($P < 0.05$ for lignocaine; $P < 0.001$ for mepivacaine). Significant vasoconstriction was only observed for cinchocaine at 0.01% ($P < 0.05$) and prilocaine at 1.0% ($P < 0.001$), compared with saline. Vasoconstrictor activity declined with increasing concentration for lignocaine, mepivacaine and cinchocaine, although this trend was not significant.

Taking the results for both ester agents together, 108 out of 120 blebs showed vasodilatation, compared with 49 out of 240 blebs for the four amide agents combined ($P < 0.001$).

Analgesic activity

For each time of testing, the mean pinprick score for the 10 subjects was converted to a percentage (full recovery = 100%). Figure 2 is a graphical representation of these results with time, for all three concentrations of the six agents, and for saline. The analgesic activity of 0.1% prilocaine and 0.01% cinchocaine differed little from that produced by saline. There was no difference between the analgesic activity of 0.1% and 0.3% procaine, but in all other instances analgesic activity increased with concentration. Only 1.0% lignocaine produced complete analgesia (0% recovery in all subjects at 10 min). A comparison of figures 1 and 2 demonstrates that there was no relationship between vasoactivity and initial analgesic activity.

Duration of action

Complete recovery from all injections (permanent pinprick score of 5 in all subjects) had occurred by 80 min. The mean 50% recovery times of the different concentrations of the six agents plotted against the concentration on a logarithmic scale is shown in figure 3. The concentrations used were chosen to lie on the central linear portion of the respective log dose–duration curves; this appears to have been achieved with all agents except procaine, although the lowest concentration of procaine still had a 50% recovery time well above that of the control solution.

Figure 4 shows the regression lines of log concentration *v.* duration of action for each agent; concentration is expressed as a multiple of the lowest concentration to eliminate differences in potency. There was a highly significant difference between the slopes ($P < 0.001$; F test). In general, the steepness of the slope reflected the observed vasoactivity of the agent; there was a significant difference ($P < 0.05$) between the slopes of procaine and mepivacaine, cinchocaine and prilocaine, and between those of amethocaine and mepivacaine.

DISCUSSION

The relationship between the vasoactivity of a local anaesthetic agent and its duration of action is not straightforward. Using the intradermal route, in which systemic, reflex and regional effects are eliminated, Aps and Reynolds (1976) found a greater incidence of vasoconstriction with 0.125% bupivacaine than with 0.25% bupivacaine; the duration of action was not significantly different, indicating that the effect of increasing concentration was counteracted by the reduced vasoconstriction. L(−) Bupivacaine was longer acting than D(+) bupivacaine in concentrations of 0.48–3.84 mmol litre^{-1} (0.16–1.25%), and over this range, the L(−) isomer showed significantly greater vasoconstriction (Aps and Reynolds, 1978). Luduena (1969), also, concluded that the increased duration of action of L(+) prilocaine, L(+) mepivacaine and L(−) bupivacaine, compared with their optical isomers, was solely attributable to the production of greater vasoconstriction. In contrast Fairley and Reynolds

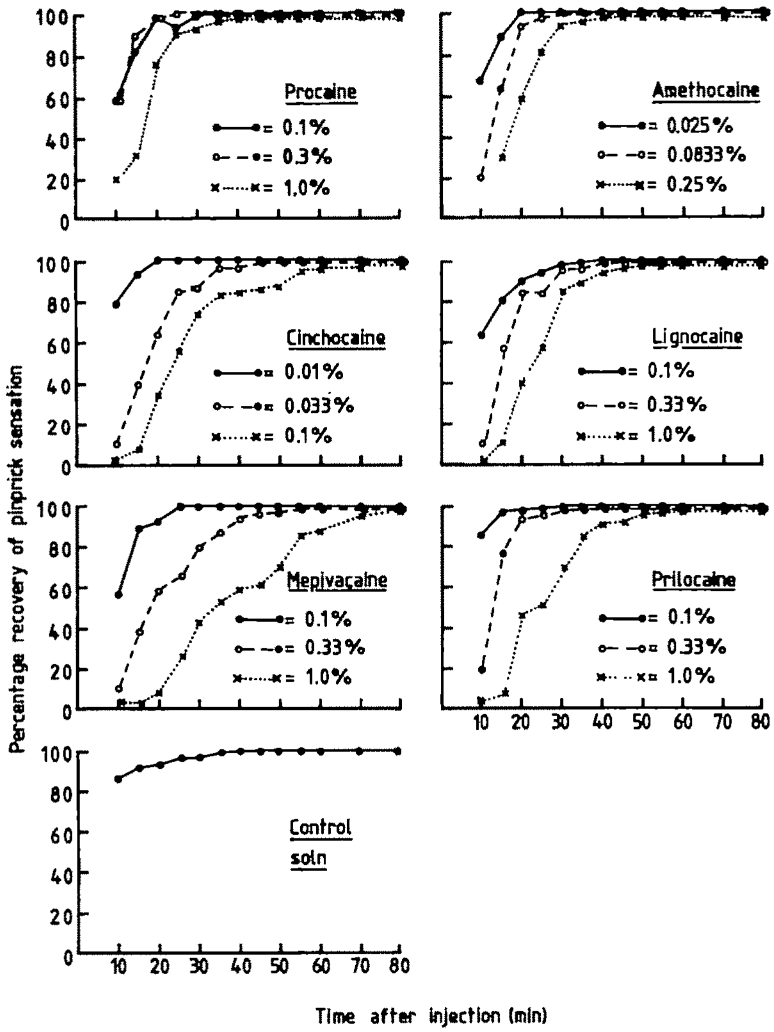

FIG. 2. Mean pinprick scores presented as percentage recovery against time for each concentration of the six agents tested. $n = 20$ for each point, except for the control solution where $n = 40$.

(1981), comparing L(+) and D(−) mepivacaine, found that the increase in the duration of action of the L(+) isomer in concentrations of 0.1–0.9% was not associated with greater vasoconstriction; indeed, at the highest concentration L(+) mepivacaine was the more potent vasodilator. In the present study, the vasodilatation produced by procaine and amethocaine, and the vasoconstriction seen with mepivacaine, were associated with differences in the mean slope of the log dose–duration plots in the expected direction compared with cinchocaine, lignocaine and prilocaine, with which the vasoactivity was less marked and more variable. With none of the six agents was the vasoactivity as concentration-dependent as in previous intradermal studies (Aps and Reynolds, 1976; Reynolds, Bryson and Nicholas, 1976; Fairley and Reynolds, 1981). This may have been the result of the presence of sodium metabisulphite in the solutions; certainly, the saline–metabisulphite control solution produced a much higher incidence of vasodilatation (65%) than had been observed previously with plain 0.9% saline (0–10%). The addition of metabisulphite also appeared to increase the pain of the injection.

There are few reports of the effects of the intradermal administration of ester-linked local anaesthetics in man. Padfield (1967) compared 2%

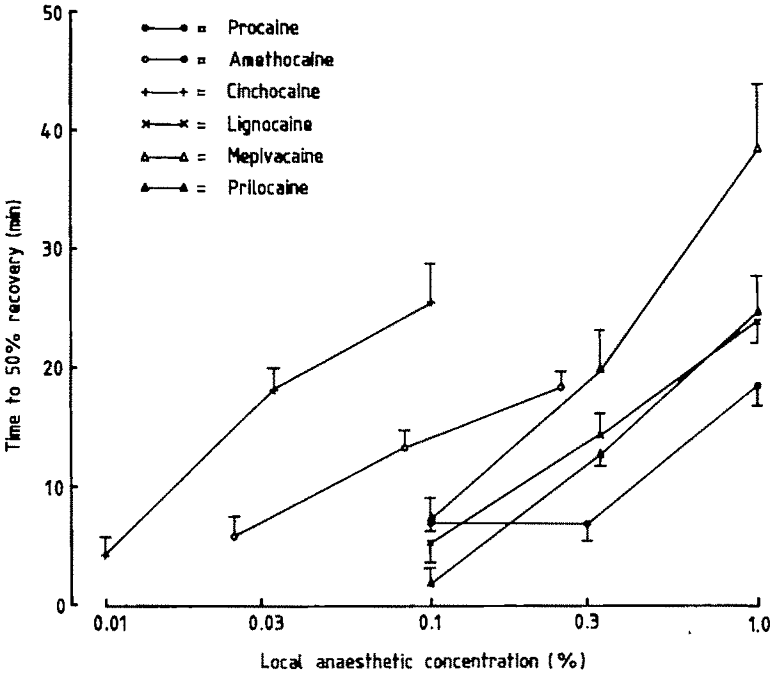

FIG. 3. Mean duration of action (expressed as time to 50% recovery) for each of the six local anaesthetic agents tested. $n = 10$ for each point. Vertical bars represent SEM.

prilocaine, 2% lignocaine and 2% procaine intradermally in human volunteers and found that these agents were equi-analgesic shortly after injection, with procaine having the shortest, and prilocaine the longest duration of action. There was a 60% incidence of vasodilatation with procaine. The action of ester-linked local anaesthetics on other vascular tissues, as well as on smooth muscle from other organs, appears to vary. In the rabbit aortic strip preparation, the contraction produced by acetylcholine, histamine, noradrenaline or 5-hydroxytryptamine was inhibited in a dose-dependent manner by procaine and amethocaine in concentrations ranging from 1 μmol litre^{-1} to 1 mmol litre^{-1}, although the potencies for these inhibitory actions were not related to local anaesthetic potency (Altura and Altura, 1974). It was postulated that these effects

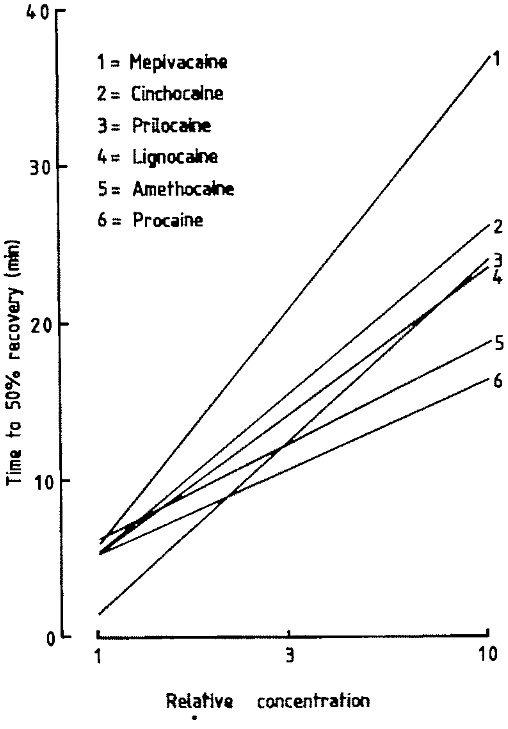

FIG. 4. Mean regression lines for duration of action calculated by the GLIM3 linear modelling computer. Concentration expressed as multiples of the lowest concentration for each agent. Slope values (min per log unit of concentration) ± SEM: Procaine, $b = 11.41 \pm 2.31$; amethocaine, $b = 12.77 \pm 2.12$; lignocaine, $b = 18.47 \pm 2.53$; cinchocaine, $b = 21.05 \pm 2.94$; prilocaine, $b = 22.70 \pm 3.09$; mepivacaine, $b = 31.12 \pm 5.51$.

might be mediated by "alteration in intracellular metabolism".

Jacobs and Keating (1974) demonstrated that procaine, in concentrations up to 20 mmol litre^{-1}, facilitated or induced electrical and mechanical activity in sheep carotid artery strips, but in high concentration (80 mmol litre^{-1}) blocked electrical activity and caused contraction followed by relaxation. Blockade of Ca^{2+} entry channels was thought to be the mechanism for the relaxant effect; procaine is known to inhibit Ca^{2+} exchange in uterine smooth muscle (Feinstein, 1966). Åberg (1972) suggested that the smooth muscle relaxant effect of high concentrations of local anaesthetics is the result of inhibition of Ca^{2+} release by stabilization of the membrane surrounding Ca^{2+} stores.

The local oedema that we observed frequently with amethocaine may have decreased capillary blood flow and retarded absorption (Luduena, 1969). However, our results do not support this; any such effect may have been counteracted by the vasodilatation observed; in no instance was the weal blanched.

The duration of action of procaine and amethocaine might be decreased by plasma cholinesterase acting locally. However, Foldes and McNall (1952) found that the duration of action of procaine and chloroprocaine, given via the intradermal route in man, was not prolonged by the addition of a plasma cholinesterase inhibitor either with or without adrenaline. This indicates that, intradermally, *in situ* hydrolysis of ester-linked local anaesthetics is not a factor determining the duration of action.

It would appear that vasodilatation is a feature of ester-linked local anaesthetics even at low concentrations, in contrast to amides. In the clinical setting, intrinsic vasoconstriction enhances local anaesthetic activity while diminishing toxicity and, thus, contributes to the superior performance of the amides.

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pH-DEPENDENT ACCUMULATION OF FENTANYL, LOFENTANIL AND ALFENTANIL BY BEATING GUINEAPIG ATRIA

H. LÜLLMANN, B.-S. MARTINS AND T. PETERS

SUMMARY

The influence of the pH of the incubation medium on the cellular accumulation of tritiated fentanyl, lofentanil, and alfentanil was investigated in isolated guineapig atria. Fentanyl and lofentanil accumulated in atrial tissue up to about 30- and 50-fold, respectively. The amount of drug bound when equilibrium was attained was found to be dependent upon the pH of the medium. By plotting binding equilibria v. *pH of the bath, curves were obtained which resembled titration curves. Half-maximal binding was attained at pH values close to the* pK_a *values of fentanyl and lofentanil. Alfentanil was found to accumulate less. The uptake by the tissue was strongly proportional to the extracellular concentration. Atria equilibrated with fentanyl at pH 8.5 released the compound rapidly when exposed to a pH of 7.0, even in the continuous presence of fentanyl in the bath. The consequences of the findings for* in vivo *conditions are discussed with respect to a possible augmentation of the actions of fentanyl by respiratory acidosis.*

Fentanyl, a potent opioid, is used widely during general anaesthesia. It contains an ionizable nitrogen which, according to its pK_a, undergoes dissociation within physiological and pathological pH ranges. As a result, the tissue distribution of fentanyl should depend critically upon the fraction which is ionized, since the water and lipid solubility of the free base, and of the charged form of the drug, differ markedly.

The present study was prompted by two considerations: first, there are several reports which describe an augmentation of the action of fentanyl when artificial ventilation is terminated at the end of surgery (Becker et al., 1976; Stoeckel, Hengstmann and Schüttler, 1979; McQuay et al., 1979; McClain and Hug, 1980). The enhanced activity is accompanied by an increase in the plasma concentration of fentanyl ("secondary peak"). Second, the recent availability of two congeners of fentanyl which differ from the mother compound with respect to hydrophobicity (lofentanil) or both pK_a and hydrophobicity (alfentanil).

To study the distribution of these opioids between an aqueous phase and tissue we used isolated, electrically stimulated guineapig atria which were shown to contract in the pH range 7.0–8.5. An intact function of the chosen tissue was considered essential since, otherwise, the accumulation of the drugs might be altered by damaged cells.

MATERIALS AND METHODS

Left atria of guineapigs (weight range 300–350 g) were rapidly dissected and, after having a weight of 500 mg attached, were placed between stimulation electrodes (frequency 3 Hz) in a 500-ml organ bath. The incubation medium consisted of a modified Krebs–Henseleit solution with the following composition (mmol $litre^{-1}$): sodium chloride 117; potassium chloride 4.5; calcium chloride 0.5; glucose 5; and Tris-buffer 30, and was gassed by pure oxygen. The desired pH was

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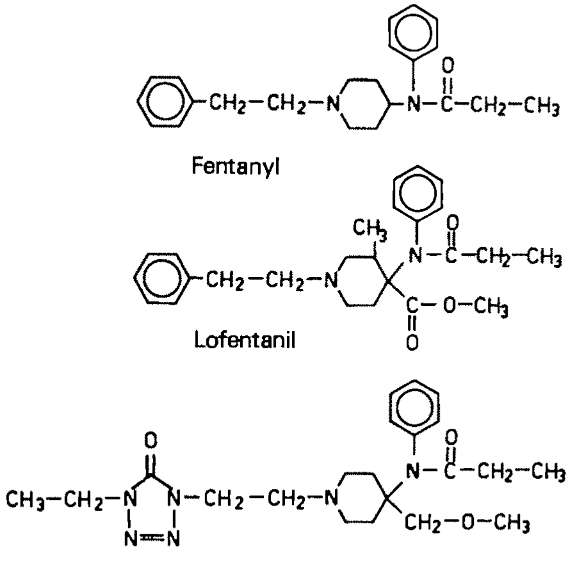

FIG. 1. Structural formulae of fentanyl, lofentanil and alfentanil.

adjusted with hydrochloric acid and carefully monitored during the entire investigation.

The specific activity of the randomly tritiated opioids (fig. 1) was 11 Ci mmol^{-1} for fentanyl, 30.3 Ci mmol^{-1} for lofentanil and 23.1 Ci mmol^{-1} for alfentanil. The radiolabelled compounds were diluted by the corresponding unlabelled drugs to yield appropriate counts at a given concentration.

After an equilibration period (in bath) of at least 1 h, the atria were transferred to an organ bath containing an identical milieu, but with the addition of the radiolabelled compound. After different periods of time the atria were removed, blotted, weighed and dissolved by Soluene (Packard Instruments). The radioactivity was counted by means of a liquid scintillation counter (Packard Instruments). The radioactivity in counts per minute/g wet tissue (T) was related to the radioactivity present in the incubation medium (M) (counts per minute/ml medium) and expressed as tissue:medium ratio (T/M), which was a measure of the accumulation of drug. The fraction of the drug present in the extracellular space was not accounted for, since it was not possible to estimate the amount possibly bound to macromolecules.

The release of the drugs from atrial tissue was studied in atria which were incubated in a solution containing radio-labelled fentanyl until the distribution equilibrium was attained. Thereafter the atria were transferred to baths containing solutions of differing pH with or without the drug.

RESULTS

Fentanyl

The accumulation of fentanyl 1×10^{-7} mol litre^{-1} was investigated at four different pH values. As shown in figure 2, the final distribution equilibria seemed to be reached after 2 h of exposure. The extent of accumulation depended markedly on pH; approximate values of T/M were: 7 at pH 7; 13 at pH 7.4; 25 at pH 8.0 and 30 at pH 8.5. Plotting the equilibria of accumulation (T/M values) measured at different pH values against the pH of the incubation medium (see inset, figure 2) a curve which displayed the characteristics of a titration curve was obtained and this permitted estimation of the apparent pK_a which corresponded to the turning-point of the curve. The pK_a of fentanyl resulting from this biological investigation was 7.7.

The release of fentanyl from the atrial tissues was studied by loading them at a pH of 8.5 and transferring the atria to a medium at pH 7.0. In figure 3 the equilibrium accumulation is set equal to 100% (corresponding to a T/M value of about 30). Under the conditions of both decrease in pH and removal of fentanyl, the drug was released from the tissue rather rapidly: by 10 min about 65% of the accumulated radioactivity had been lost. Reducing the pH to 7.0, in the presence of fentanyl, release was somewhat delayed, but the drug still left the tissue rapidly: by 10 min about 50% and by 30 min about 70% of the accumulated compound had been re-distributed.

Lofentanil

Compared with that of fentanyl, the lipophilicity of lofentanil was higher, although the pK_a lay in the same range. As demonstrated in figure 4, again at four pH values in the incubation medium, lofentanil 1×10^{-7} mol litre^{-1} accumulated markedly and the degree of accumulation was dependent on the proton concentration. The equilibria attained after 2–3 h were about twice as high as those determined for fentanyl. These degrees of accumulation by the tissue are in good agreement with the partition coefficients (H_2O/octanol) determined for fentanyl ($\log P = 4.05$) and for lofentanil ($\log P = 4.22$).

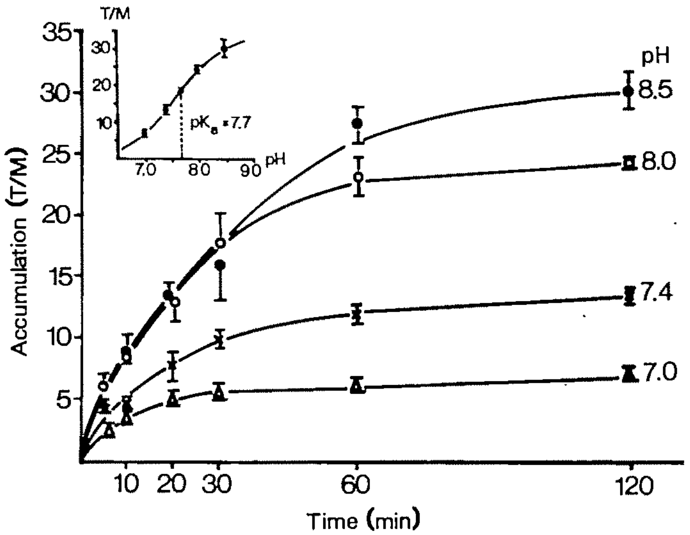

FIG. 2. Uptake of fentanyl 10^{-7} mol litre^{-1} by isolated guineapig atria at different pH. Accumulation expressed as tissue:medium ratio (T/M). Means ± SEM; $n = 3$. Inset: T/M at equilibrium plotted *v.* pH of incubation medium yielding an apparent pK_a of about 7.7.

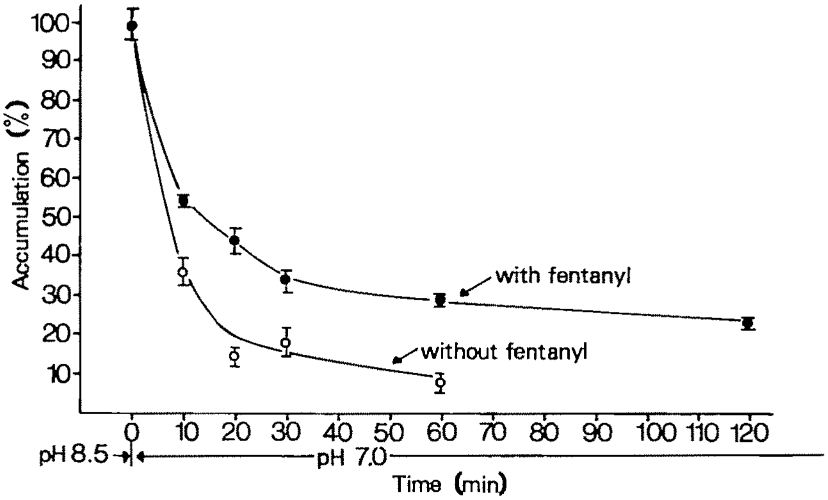

FIG. 3. Release of fentanyl from isolated guineapig atria after preincubation with fentanyl 10^{-7} mol litre^{-1} at pH 8.5 for 2 h. The release occurs after changing the pH to 7.0 at zero time. Open circles: no fentanyl present in the medium; filled circles: fentanyl still present at a concentration of 10^{-7} mol litre^{-1}. Abscissa: time in minutes after pH change. Ordinate: tissue accumulation of fentanyl set equal to 100% corresponding to a tissue medium ratio of about 30.

The graph of tissue accumulation (T/M) *v.* pH of the medium yielded a "titration curve" (see inset, fig. 4) which allowed estimation of the apparent pK_a of lofentanil — 7.6.

Alfentanil

Compared with the other two drugs, alfentanil was more hydrophilic and its pK_a was 6.5 and, thus, was below the physiological pH range. The uptake of alfentanil 1×10^{-7} mol litre^{-1} was investigated at pH values in the medium of 8.0, 7.0, and of 6.5, although the contractile force of the atria was decreased to about 10% of that of control at the acid pH. In spite of the decrease in contractility, the atria contracted regularly following stimulation at a frequency of 3 Hz. The uptake curves

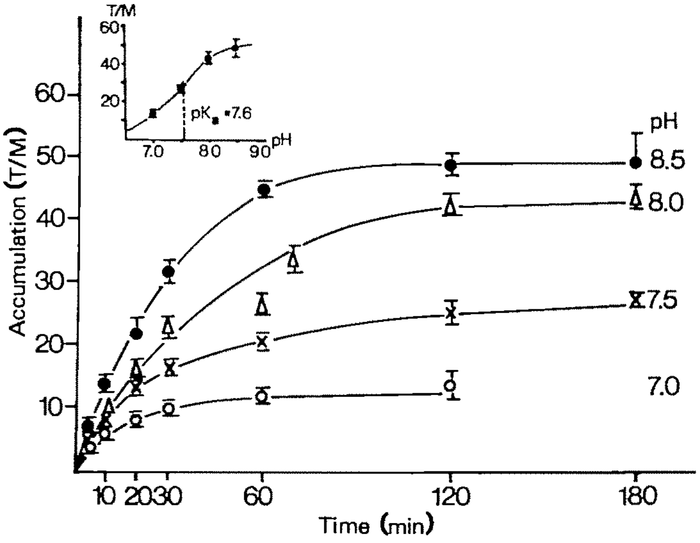

FIG. 4. Uptake of lofentanil 10^{-7} mol litre^{-1} by isolated guineapig atria at different pH. Accumulation expressed as tissue:medium ratio (T/M). Means ± SEM; $n = 3$–5. Inset: T/M at equilibrium plotted *v*. pH of incubation medium yielding an apparent pK$_a$ of about 7.6.

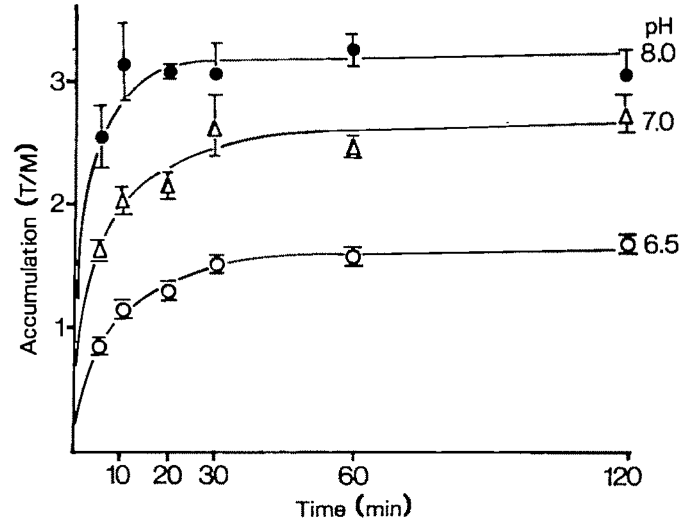

FIG. 5. Uptake of alfentanil 10^{-7} mol litre^{-1} by isolated guineapig atria at different pH. Accumulation expressed as tissue:medium ratio (T/M). Means ± SEM; $n = 3$–6. Note the altered ordinate.

obtained at the different pH values are depicted in figure 5. Equilibria were reached much more rapidly, and the accumulation was much less than in the cases of fentanyl or lofentanil. The maximal accumulation of alfentanil at pH 8, at which alfentanil was totally present as a free base, amounted to a T/M value of 3. At a pH of 6.5, corresponding to the pK$_a$ of 6.5, the accumulation was decreased to about one-half. This again suggests that only the free base is able to accumulate and not the ionized molecule.

Since the accumulation of alfentanil was small, we used this compound to investigate the concentration-dependent accumulation at a given pH. If saturable binding was present in addition to the unspecific binding, then the likelihood of detecting it would be greatest with alfentanil. In figure 6 the uptake curves for four different

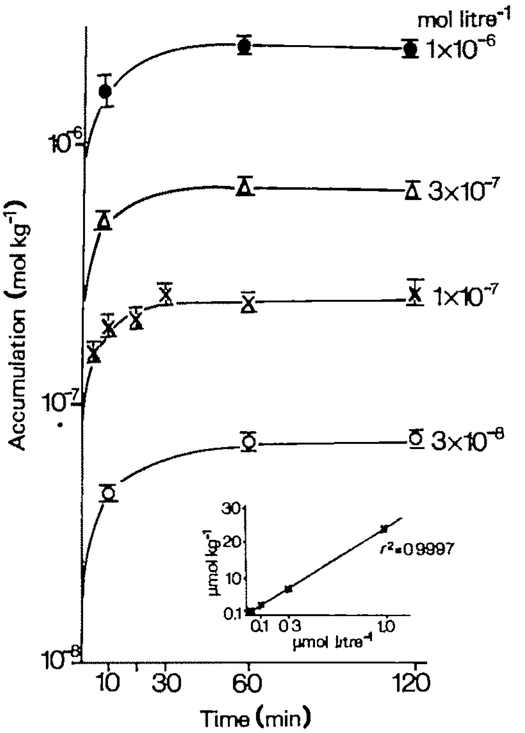

FIG. 6. Concentration-dependent accumulation of alfentanil by guineapig atria at constant pH 7.0. Concentrations are indicated on the curves. Accumulation in mol kg^{-1} w.w. Inset: accumulation at equilibrium plotted *v.* concentration of alfentanil in the medium. Means ± SEM; $n = 3$.

concentrations of alfentanil (3×10^{-8}–1×10^{-6} mol litre^{-1}) at a pH of 7.0 are demonstrated. Plotting the maxima *v.* the concentrations (see inset, fig. 6) yielded a straight line which indicated that the accumulation was proportional to the concentration. There was no indication for a saturable component within this concentration range, suggesting that fentanyl and its analogues are distributed solely according to physico–chemical forces.

DISCUSSION

The tissue distribution of ionizable drugs depends upon their water and lipid solubility and upon their pK_a. If the pK_a of a certain drug lies close to or within the physiological pH range, the distribution will be susceptible to changes in pH, since the solubility of the ionized and the non-ionized forms of the drug may differ widely. This has been demonstrated for the amphiphilic compound fentanyl and the congeners lofentanil and alfentanil in the present study. (The term amphiphilic denotes that a compound possesses hydrophilic and hydrophobic properties within a short molecular range.)

Fentanyl and lofentanil possess similar pK_a values, but differ with respect to their partition coefficients. This is reflected in similar pH dependencies of the accumulation curves, and by the greater accumulation of lofentanil. By extrapolation, accumulation by atrial tissue of the free base of fentanyl of about 30, and of the free base of lofentanil of about 50 could be estimated. In contrast, the more hydrophilic alfentanil only accumulated about 3-fold. Its pK_a of 6.5 did not allow us to evaluate the pH dependency of accumulation completely, since atrial tissue remained functioning only in the pH range (6.5) 7.0–8.5. The tissue binding of alfentanil at different concentrations proved to be proportional to the applied concentrations, suggesting the absence of additional saturable binding sites within the investigated concentration range. When atria were equilibrated with fentanyl at a pH of 8.5 and then transferred to a medium of pH 7.0 containing the identical overall concentration of fentanyl, a re-distribution proceeded rapidly and resulted in a loss of half of the accumulated fentanyl within 10 min.

If it is assumed that atrial tissue is representative with respect to the accumulation of fentanyl, the following consideration emerges (fig. 7): at equilibrium fentanyl will be present in three forms (free base, ionized, and bound) in the plasma and in the interstitial fluid. Tissue accumulation depends on the concentration of free base present in the interstitial fluid, which in turn is highly dependent on the actual pH (fig. 2). At a pH of 7.4, fentanyl will accumulate about 13-fold. Taking into account the sizes of the different spaces, the fractions of a given dose present in the different spaces can be calculated roughly: about nine-tenths will be bound to cellular structures and hidden in a deep compartment not participating in the pharmacological effect. Only the concentration of the ionized fentanyl within the interstitial fluid will determine the effect by interacting with opioid receptors facing the extracellular space.

Drug distribution of the kind just outlined has two significant consequences from a clinical point of view. (1) The distribution and, consequently, the concentration of the particular pharmacologically active drug will be highly susceptible to pH changes. For instance, acidosis occurring after the termination of artificial ventilation will induce a massive shift from the free base towards the

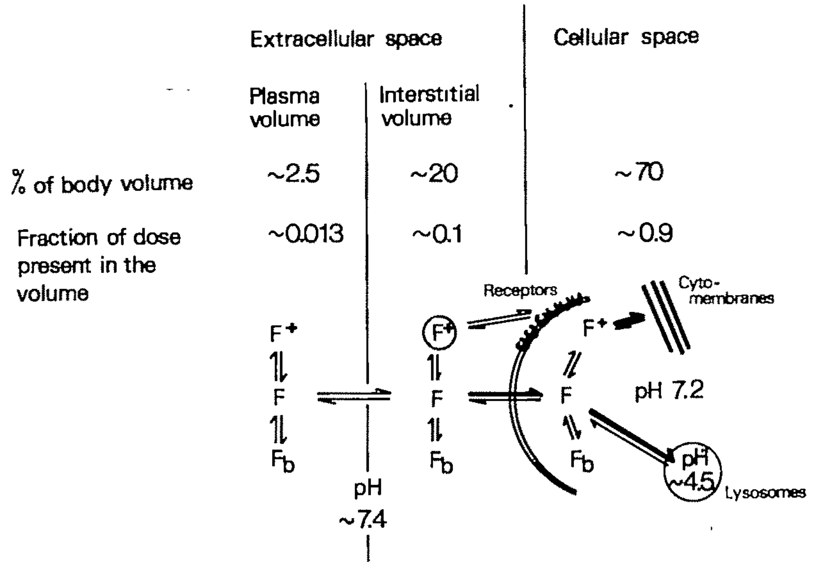

FIG. 7. Distribution of fentanyl within the body compartments at an extracellular pH of 7.4. The accumulation of fentanyl by the tissue is assumed to be 13-fold (see Results). In the extracellular space an equilibrium exists between the ionized fentanyl (F^+), the free base (F) and the fentanyl molecules bound to macromolecules (F_b). The concentration of ionized fentanyl within the interstitial fluid (encircled F^+) determines the pharmacological effect since the opioid receptors (◡◡) are located at the cell surface. Fentanyl as free base readily penetrates into the cells and becomes bound to cytomembranes, lysosomes and other structures (thick arrows), and, thus, accumulates in the cell. A small decrease of the extracellular pH will shift the equilibrium between F and F^+ towards higher F^+ concentrations and will induce a marked release of fentanyl from the cellular compartment as a result of the decrease of the concentration of F in the interstitium. An increase of the extracellular H^+ concentration by pH 0.2 might roughly double the concentration of ionized fentanyl within the interstitial fluid and accordingly enhance its pharmacological effect.

ionized form of fentanyl and induce a release of fentanyl from the cells supporting this process. The result will be an augmentation of the actions of fentanyl which, in turn, might suppress the respiratory centre, increase the acidosis and further increase the plasma concentration of ionized fentanyl. (2) The elimination of fentanyl will proceed rather slowly, since the actual concentration of free fentanyl present in the plasma (renal excretion) and in the interstitial fluid (metabolic degradation by the liver) is very low as a result of the large fraction accumulated by tissues. The tissue store of fentanyl will be released slowly and will follow the decrease in the extracellular free base concentration.

The considerations concerning the pharmacokinetics of fentanyl will also apply to lofentanil. It will be highly susceptible to pH changes occurring during its administration, and its elimination will be even slower, since it accumulates more markedly than fentanyl. In the case of alfentanil, tissue accumulation plays only a minor role. Its pK_a lies outside the physiological pH range and makes it less susceptible to changes in pH. From a physico-chemical point of view, alfentanil should compare favourably with fentanyl; however, further clinical experience must be awaited.

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Br. J. Anaesth. (1985), 57, 1018–1021

INTERACTIONS BETWEEN DILTIAZEM AND ISOFLURANE

An In Vitro *Investigation in Isolated Guineapig Atria*

M. P. BROADBENT, P. C. SWAN AND R. M. JONES

SUMMARY

Maximum force of contraction of paced, isolated guineapig atria was measured in three groups. Atria from animals in group 1 were exposed to isoflurane for 10 min. In group 2, atria were exposed to diltiazem 35 nmol litre^{-1} alone and in group 3 atria were pre-treated with diltiazem 35 nmol litre^{-1} before exposure to isoflurane. Maximum depression of contraction was significantly greater in tissue exposed to the combination of diltiazem and isoflurane (group 3) compared with that exposed to isoflurane alone (group 1). Tissue exposed to diltiazem and isoflurane remained significantly more depressed from 15 to 30 min after the administration of isoflurane compared with the depression produced by the volatile agent alone. The results suggest that the calcium antagonist, diltiazem, may modify the effects of isoflurane on myocardial function.

Although the mechanisms underlying the negative inotropic effects of volatile anaesthetic agents are not completely understood, they appear to be related to changes in ionic flux, principally those involving calcium. Calcium antagonist drugs, which are being used more frequently in a variety of cardiovascular disorders, have diverse sites of action and varying effects on cellular and transcellular calcium kinetics. A delay in the recovery of halothane-induced depression of *in vitro* papillary muscle pre-treated with verapamil (Caplan and Su, 1984) suggests that calcium antagonists and volatile anaesthetic agents may act synergistically to impair the reversibility of myocardial depression. We have studied the interaction between the calcium antagonist diltiazem and the volatile anaesthetic agent isoflurane in an isolated *in vitro* preparation to determine whether this combination (which current evidence suggests should have the least effect, if any, on the heart) influences the maximum force of contraction (F_{max}) of myocardial muscle.

METHODS AND MATERIALS

Twenty-one male Dunkin–Hartley guineapigs were assigned to one of three groups: (1) to receive isoflurane at the minimum alveolar concentration (MAC) reported for man (1.1%), (2) to receive diltiazem 35 nmol litre^{-1} and (3) to be exposed to isoflurane after prior exposure to diltiazem.

Animals were killed and the atria were dissected into cold (0–2 °C) modified Ringer–Locke solution (composition in mmol litre^{-1}: NaCl 143; KCl 5.6; glucose 5; $NaHCO_3$ 23; $CaCl_2$ 2.6). Weights of the animals and of the dissected atria are shown in table I. Ties were attached to the tips of each atrium and the preparation was transferred to an organ bath containing Ringer–Locke solution maintained at a temperature of 34 °C and aerated with 100% oxygen. Fresh gas flow in the organ bath was maintained at a constant 200 ml min^{-1}. One atrial tie was attached to a fixed point in the bath, drawing the tip of the right atria into contact with a stimulating electrode: the other tie was attached to an isometric force transducer (Ormed, Type 4155). The atria were paced at a frequency of 3.5 Hz with square-wave d.c. impulses of 1 ms duration at a voltage sufficient to over-pace the natural rhythmicity. When a stable pattern of contractile force was observed, a control period of F_{max} was recorded.

Atria from animals in group 1 were exposed to isoflurane after 10 min of control readings, the anaesthetic agent being introduced to the organ bath via the aeration circuit by means of a calibrated vaporizer. The concentration of the

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TABLE I. *Details of groups studied*

	Animal weights (g)			Tissue weights (g)		
	Mean	SD	Range	Mean	SD	Range
Group 1 Isoflurane alone ($n = 6$)	542	90	426–689	0.245	0.013	0.224–0.261
Group 2 Diltiazem alone ($n = 7$)	550	64	459–630	0.247	0.009	0.232–0.263
Group 3 Diltiazem + isoflurane ($n = 7$)	525	46	490–609	0.228	0.010	0.217–0.242

anaesthetic agent was monitored throughout the experimental period (Engstrom Emma, standardized with a calibrating sensor). After 10 min of exposure, the administration of isoflurane was discontinued and the tissue tension monitored for a further 30 min. In group 2, atria were exposed to a bath equivalent of diltiazem 35 nmol litre^{-1} and were continuously monitored for 50 min. Group 3 atria were pre-treated with diltiazem 35 nmol litre^{-1} for 10 min, were exposed to isoflurane for a further 10 min and were then monitored for another 30 min. Results are expressed in terms of F_{max} as a percentage of the control stabilized F_{max} (mean($\pm$SD)) and were analysed, where appropriate, using the unpaired t statistic.

RESULTS

The maximum depression of F_{max} produced by isoflurane alone was 69($\pm$8)% of control and occurred 20 min after the initial exposure of the tissue to the volatile agent, that is 30 min after the start of the experimental period (t_{30}). Diltiazem alone caused a significant decrease in F_{max} at t_{15} (96% of control) and this continued for the duration of the exposure and reached a maximum of 77% after 50 min.

Atria exposed to both diltiazem and isoflurane were depressed maximally 35 min after the addition of the calcium antagonist (25 min after the introduction of the volatile agent to the organ bath). The maximum depression of F_{max} produced by diltiazem and isoflurane in combination was significantly ($P < 0.001$) different from that produced by isoflurane alone and this maximal depression of the combined agents occurred 5 min later than the depression produced by isoflurane alone. The greater depressive effect of the combination of diltiazem and isoflurane was maintained from t_{35} to t_{50} and this depression was significantly different from that produced by isoflurane alone ($P < 0.02$ at t_{35} and t_{40}, $P < 0.05$ at t_{45} and t_{50}). Table II shows values of maximum force of contraction for the three groups and these results are displayed graphically in figure 1.

DISCUSSION

Several of the fundamental physiological processes of the myocardial cell are mediated by calcium ions. Surface excitation is linked to muscular contraction by the slow inward current of the cardiac action potential, which is principally carried by calcium ions. The precise mechanisms linking excitation to contraction and the essential role of calcium are complex. A number of steps, such as the mechanism of calcium release upon excitation, are as yet unexplained. The compartmentation of calcium within whole myocardial tissue and the sarcolemmal location for most of the rapidly exchangeable fractions have recently been reviewed by Langer (1983).

Both calcium antagonists and volatile anaesthetic agents interfere with normal calcium ion flux within myocardial muscle fibres. Lynch (1984) describes the action of the calcium antagonists as demonstrating slow (calcium) channel-blocking effects whereas the volatile anaesthetics alter calcium control and excitation–contraction coupling in the myocardium at several levels. The number of slow channels, selectively blocked by

TABLE II. *Maximum force of contraction (percentage of control) of isolated guineapig atria exposed to isoflurane (group* 1), *diltiazem (group* 2) *and diltiazem + isoflurane (group* 3). (*SD values in parentheses*)

	Time (min)										
	0	5	10	15	20	25	30	35	40	45	50
Group 1											
Isoflurane alone ($n = 6$)	100	100	99 (1)	94 (5)	84 (9)	71 (5)	69 (8)	73 (9)	77 (11)	80 (13)	85 (14)
Group 2											
Diltiazem alone ($n = 7$)	100	100	98 (2)	96 (2)	94 (3)	90 (3)	87 (3)	83 (3)	80 (3)	78 (4)	77 (4)
Group 3											
Diltiazem + isoflurane ($n = 7$)	100	100	99	93 (2)	86 (4)	71 (3)	64 (3)	58 (4)	59 (3)	63 (5)	66 (4)

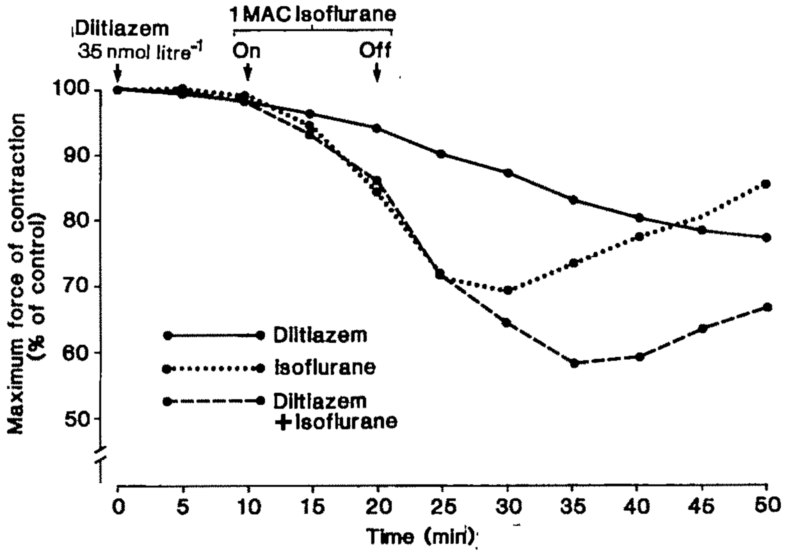

FIG. 1. Graph of maximum force of contraction (F_{max}) as a percentage of control in the three groups (diltiazem alone, isoflurane alone and diltiazem + isoflurane).

the calcium antagonists, that can be voltage activated is modified by the cyclic-AMP dependent kinase system and this in turn may be influenced by the volatile anaesthetic agents.

It is now reasonably well established that the myocardial depression produced by all modern volatile agents is related, at least in part, to alterations in calcium ion flux (Jones, 1985), and Blanck and Thompson (1982) have predicted that volatile anaesthetics will be found to have very small, but significant, effects at several sites in the excitation–contraction mechanisms and, consequently, depress contractility. Isoflurane-induced myocardial depression is partly caused by the decreasing calcium activation of the contractile proteins (Su and Bell, 1982), and it is also noted that the effects of isoflurane in this respect are much less than those of halothane or enflurane.

Studies using intact animals have suggested that diltiazem has little effect on inotropy (Millard et al., 1982; Kraynack, 1983), although Perez and colleagues (1982), also using isolated guineapig atria, demonstrated that this agent does have the potential to reduce F_{max}, but does so significantly less than the other calcium antagonists, verapamil and nifedipine. We used a bath concentration of diltiazem which is approximately 10% of the therapeutic plasma concentration in man (Kates, 1983), diltiazem being up to 90% protein bound. At this concentration we have demonstrated that, in an isolated tissue preparation, which is free of the compensatory mechanisms present in intact animals or man, diltiazem causes a minor, but reproducible, decrease in F_{max}.

We have also demonstrated that diltiazem and isoflurane interact *in vitro* in such a way that, not only is there an approximately additive decrease in contractile force, but the temporal effects of the volatile agent appear to be modified, maximum depression occurring later in the experimental period. It is known that plasma membranes bind more calcium in the presence of volatile anaesthetics, hence prior exposure to a relatively specific calcium antagonist (diltiazem) is likely to alter the interaction between plasma membranes, calcium ions and anaesthetic agents. It would appear that this interaction is altered in such a way that the onset of the decrease in F_{max} produced by isoflurane is delayed in the presence of diltiazem.

Although diltiazem and isoflurane are considered to have minimal adverse effects on myocardial contractility, we conclude that these agents, in the aforementioned concentrations, have significant and additive effects on contractile force in the isolated guineapig atria. They also interact to alter the time course of events in such a way that recovery after exposure to the volatile agent is delayed, as is the onset of the maximal decrease in F_{max}. These observations may have some clinical relevance in patients concurrently taking the calcium antagonist, diltiazem, who present for general anaesthesia.

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HAEMORRHAGE DECREASES THE ANAESTHETIC REQUIREMENT FOR KETAMINE AND THIOPENTONE IN THE PIG

R. B. WEISKOPF AND M. S. BOGETZ

SUMMARY

The anaesthetic requirements of ketamine and thiopentone were studied in eight pig littermates during normovolaemia and after haemorrhage (30% blood loss). Four animals received ketamine and four thiopentone, and the minimal anaesthetic doses of both drugs were determined. Moderate hypovolaemia decreased the anaesthetic requirements significantly and similarly: thiopentone 33±5%; ketamine 40±5% (mean±SEM).

In the hypovolaemic patient, the induction dose of an anaesthetic agent is frequently decreased so as to minimize any adverse cardiovascular effects. However, it is not clear whether such a dose produces anaesthesia. Recently, Bogetz and Katz (1984) reported that victims of major trauma who received a small dose of anaesthetic, or no anaesthetic, for "induction of anaesthesia" recalled being aware during surgery. In three dogs, Eger, Saidman and Brandstater (1965) found that haemorrhage sufficient to decrease the diastolic arterial pressure by one-half to two-thirds of its baseline value decreased the minimal alveolar concentration (MAC) of halothane by 20%. Such a decrease in MAC might be a consequence of an impairment of brain oxygenation resulting from the decrease in oxygen delivery. However, MAC was shown to decrease only when the Pa_{O_2} was less than 5.3 kPa (Cullen and Eger, 1970a); and during severe isovolaemic anaemia, only when the arterial oxygen content was less than 5 ml/dl blood (Cullen and Eger, 1970b). In other studies, the use of other drugs has been combined with anaesthetic agents, thus masking the effects of haemorrhage or hypotension alone on the requirement for anaesthesia. We have studied the effect of haemorrhage on the anaesthetic requirement for the i.v. induction agents ketamine and thiopentone.

MATERIALS AND METHODS

Eight pigs (Chester–White–Yorkshire cross littermates) (mean weight±SEM, 15.3±0.4 kg) were divided into four pairs on the basis of similarity of weight. One of each pair was randomly selected to receive thiopentone (group T) or ketamine (group K). All animals were in good health.

The animals were anaesthetized four times while normovolaemic, with at least 2 days between each study. Unpremedicated animals were placed in a sling, and a cannula inserted to an ear vein. In random order, on four separate occasions, animals in group K received ketamine 12.5, 15, 17.5 or 20 mg kg^{-1} i.v. rapidly. Group T animals received thiopentone 7.5, 10, 12.5 or 15 mg kg^{-1} i.v. rapidly. Each animal received all four doses. One week later the animals were anaesthetized four times while hypovolaemic. Unpremedicated animals were anaesthetized briefly with halothane in oxygen and nitrogen while arterial and venous cannulae were inserted. Arterial blood samples were obtained and P_{O_2}, P_{CO_2} and pH measured using appropriate electrodes. Arterial pressure was measured directly (Statham Model 23Db; Gould Model 2800 polygraph). The halothane was discontinued and the animal allowed to recover and placed in a sling. Further study was delayed until the end-tidal partial pressure of halothane, as measured by mass spectrometry, decreased to less than 0.07 kPa (0.05 MAC). To prevent hypoxia during and after blood loss, the animals received oxygen 1–2 litre min^{-1} by mask. Each animal was bled by 30% of

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its estimated blood volume (von Engelhardt, 1966) over a 30-min period. To ensure stability, we observed the animal for an additional 30 min before administering the ketamine or thiopentone. In random order, on four successive weeks, group K animals received one of four doses of ketamine i.v. rapidly: 5, 7.5, 10 or 12.5 mg kg^{-1}. Similarly, group T animals received thiopentone rapidly i.v.: 2.5, 5, 7.5 or 10 mg kg^{-1}.

Following the administration of each drug in either the normovolaemic or hypovolaemic state, the animal's response (movement or lack of movement) to a tail clamp was determined. These tail-clamp tests were performed 10, 20, 30, 45, 60, 90, 120 and 180 s after the administration of the drug. The dose of drug was deemed effective if the animal failed to respond to any application of the clamp. After evaluation of the tail-clamp tests in the hypovolaemic animals, the shed blood was re-infused i.v. through a standard blood filter. All animals appeared normal and were not anaemic before each individual study. In other pigs, we found that cardiovascular, hormonal and metabolic values 1 week after 30% haemorrhage and the re-infusion of shed blood did differ from the values in the same animal before the haemorrhage. The responses to the tail-clamp tests were analysed statistically as described by Waud (1972). In addition, the maximum dose of drug that failed to prevent movement in each animal and the minimum dose of drug that prevented the animal from moving were averaged for each animal. These averages for the four animals in each group were compared between normovolaemic and hypovolaemic states by using Student's *t* test. Differences between the two states were compared for the two drugs, using Student's *t* test.

RESULTS

Hypovolaemia decreased the mean (±SEM) minimum anaesthetic dose for both thiopentone ($P < 0.025$) and ketamine ($P < 0.01$) (table I). These decreases (thiopentone 33% ±5%, range 23–44%; ketamine 40% ±5%, range 31–53%) were not statistically different ($P > 0.2$) from each other. After haemorrhage and before the administration of the drug, (mean ± SEM) arterial blood-gas tensions were $P\text{O}_2$ 23.70±2.68 kPa; $P\text{CO}_2$ 5.59±0.16 kPa and pH 7.323±0.11. Haematocrit was 25.4±0.5%. Mean (±SEM) arterial pressure was 92±3 mm Hg 30 min after haemorrhage, 69±9 mm Hg 5 min after administration of ketamine and 68±7 mm Hg 5 min after the administration of thiopentone.

TABLE I. *Minimal anaesthetic dose (mean ± SEM) of ketamine and thiopentone in pigs during normovolaemia and after haemorrhage.* n = 4 *in each group.* **Statistically different (P < 0.05) from normovolaemic state*

Drug	Minimum anaesthetic dose (mg kg^{-1}) During normovolaemia	Minimum anaesthetic dose (mg kg^{-1}) During hypovolaemia	Reduction in minimum anaesthetic dose during hypovolaemia (%)
Ketamine	17.50±0.72	10.31±0.60*	40±5
Thiopentone	11.25±1.02	7.50±0.72*	33±5

DISCUSSION

Moderate haemorrhage (30% blood loss) produced similar decreases in the anaesthetic requirements of these two different i.v. anaesthetic agents. It is possible that some, or even all, of this decrease after hypovolaemia was the result of a higher concentration of the drug in the blood and brain resulting from the decrease in the volume of distribution. Changes in concentration of the drug at the site of action would depend upon alterations of blood flow to that site relative to differences in blood concentration (Eger, 1974).

Price (1960) predicted that after haemorrhage sufficient to decrease cardiac output by 40%, but insufficient to alter cerebral blood flow, a single i.v. injection of thiopentone would result in a higher central nervous system concentration of the drug than would a similar injection during normovolaemia. His mathematical model assumed that thiopentone would not alter tissue blood flow. However, this is not true during hypovolaemia. From Price's figure, one would estimate that the hypovolaemic condition he assumed would decrease the necessary dose of thiopentone by approximately one-third. Our finding of a 33±5% reduction in the dose of thiopentone is in accord with this, although in another series of hypovolaemic pigs in which we did measure cardiac output, this decreased by 35%. Bergman (1963) found a decrease in the plasma concentration of thiopentone in dogs subjected to haemorrhage 5–90 min after a 2-min injection. Thiopentone, however, disappears very rapidly from plasma and richly-perfused organs, such as the brain. Five minutes after its administration, the concentrations of drug in the central pool and in the rapidly-perfused viscera were less than 10% and 50% of their respective peak concentrations; and 60 min after injection, concentrations in both compartments were less than 5% of the peak values (Price et al., 1960). Peak concentrations of drug in the brain and the maximum anaesthetic effect occur within the first 2 min after injection. Since thiopentone rapidly leaves the areas of interest, Bergman's attempts to extrapolate from small concentrations measured much later would be subject to error. This would be further compounded as the drug's effect on haemodynamics changed with changing concentrations in various compartments. Bergman did not measure arterial pressure or cerebral blood flow. It is possible that, with the decrease in arterial pressure that may have occurred within a few minutes of the administration of thiopentone to his hypovolaemic animals (Weiskopf et al., 1984), cerebral blood flow decreased, thus decreasing the washout of the drug and decreasing its plasma concentrations. This is possible, because 15–45 s after injection, the concentration of the drug in richly-perfused tissue is greater than in arterial plasma (Price et al., 1960; Saidman, 1974).

Other factors present during hypovolaemia could alter the effective concentration of thiopentone. Thiopentone is extensively bound to serum albumin (Goldbaum and Smith, 1954). Thus, the dilutional hypoproteinaemia that occurs as compensation for haemorrhage intensifies the anaesthetic effect of thiopentone. Similarly, since any decrease in pH decreases the protein binding of barbiturates (Goldbaum and Smith, 1954), acidaemia after haemorrhage would have a similar effect.

Unfortunately, we did not measure drug concentrations in either plasma or brain and, thus, cannot confirm or refute Price's predictions, or our own speculations regarding thiopentone during hypovolaemia.

Although other variables could affect the amount of drug required to produce anaesthesia (Eger, 1974) we were unable to study most of these because of limitations imposed by our experimental design, which was selected to address the questions: "Does hypovolaemia decrease anaesthetic requirement for induction agents; and, if so, does the decrease differ for different drugs? Consequently, we have limited physiological information from the animals to complement the finding of a decrease in anaesthetic requirement.

We do have, however, a good deal of information about 21 other awake pigs, the blood volumes of which were decreased similarly in the course of other studies (Weiskopf et al., 1984). In those animals, 30% blood loss decreased arterial pressure and cardiac output. When half of the dose of thiopentone or ketamine that produced anaesthesia during normovolaemia was administered to these animals during hypovolaemia, mean arterial pressure and cardiac output decreased further. However, the mean arterial pressure of the animals in the present study did not decrease below the value at which autoregulation was able to maintain normal cerebral blood flow, nor did these animals exhibit sufficient acidosis, hypercarbia or decreases in calculated oxygen content to account for a decrease in anaesthetic requirement during hypovolaemia.

We did not measure cerebral blood flow and, thus, cannot relate this to the anaesthetic requirement of these agents. However, since specific anaesthetic site(s) of action are not known, knowledge of global cerebral blood flow would be of limited value. Knowledge of regional or microregional (if we knew which microregion) blood flow would be more helpful. Cullen and Eger (1970a,b) related a decrease in anaesthetic requirement for halothane to a decrease in oxygen delivery to the brain, from either decreased Pa_{O_2} or severe isovolaemic anaemia. A decrease in anaesthetic requirement correlates well with the occurrence of central acidosis (Eisele, Eger and Muallem, 1967). Tanifuji and Eger (1976) found a 20% decrease in anaesthetic requirement for halothane in dogs made hypotensive to an arterial pressure of 40–50 mm Hg by a combination of trimetaphan, head-up tilt and modest haemorrhage (approximately 12% blood loss). Rao and colleagues (1981) noted a decrease in anaesthetic requirement for halothane in dogs made hypotensive by the administration of pentolinium, trimetaphan or nitroprusside, but stated that they could not find any correlation between the decrease in MAC and the decrease in carotid blood flow. In their experiments, mean arterial pressure did not decrease below 60 mm Hg, this value being above the threshold at which autoregulation can no longer maintain cerebral blood flow. However, the anaesthetic requirement for halothane decreased during the administration of all three drugs; carotid blood flow did decrease significantly in the dogs given two of the drugs, but the large variability prevented achievement of statistical significance for those in the third group. Furthermore, in the dog, carotid blood flow is not a good indication of total cerebral blood flow. Thus, the literature does not contain a definitive study relating anaesthetic requirement to cerebral blood flow.

Haemorrhage increases sympathetic activity (Chien, 1967) and the concentrations of circulating catecholamines in pigs (Weiskopf et al., 1984). Since an increase in sympathetic activity increases anaesthetic requirement, it is possible that anaesthetic requirement would be decreased even further when there is no sympathetic response to haemorrhage or when such a response is blocked.

The clinician should note that the requirement for ketamine or thiopentone is decreased during hypovolaemia, and that the administration of these drugs, even in lower doses, decreases systemic arterial pressure and cardiac output profoundly, and increases systemic lactic acidosis (Weiskopf et al., 1984).

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PARANASAL SINUSITIS: A COMPLICATION OF NASOTRACHEAL INTUBATION

Two Case Reports

S. M. WILLATTS AND D. F. COCHRANE

SUMMARY

Reports are presented on two patients who developed severe paranasal sinusitis in association with prolonged nasotracheal intubation. The likely predisposing factors are discussed.

There are many recorded complications of tracheotomy (Andrews and Pearson, 1973; Dane and King, 1975; Friman, Hedenstierna and Schildt, 1976) and nasotracheal intubation is becoming used more widely (Harrison and Tonkin, 1968; Via-Reque and Rattenborg, 1981; Pippin, Short and Bowes, 1983). However, since the disadvantages as well as the advantages of any technique which attempts to replace tracheotomy should be considered before it can achieve acceptance, we report two cases of an hitherto little recognized complication of extended nasotracheal intubation: severe paranasal sinusitis.

Patient 1

A 17-year-old female was admitted on November 22, 1982 with severe head and chest injuries, plus fractures to pelvic and other bones. She was shocked, unconscious and required resuscitation. The subsequent development of the adult respiratory distress syndrome (ARDS) was treated with steroids and mechanical ventilation. A 7.5-mm nasal Portex cuffed tracheal tube was passed. On November 26, 1982, she became febrile, but no organisms were cultured from repeated specimens and platelet concentration remained normal. An infected haematoma was suspected. On November 29, 1982 her right eye was noticeably swollen and an ophthalmic opinion was sought. Clinically, periorbital oedema with proptosis was marked on the right side, less so on the left. On November 30, 1982 the patient was still febrile and unwell. It was then that an association between the nasal tube and her infection was suspected. X-rays of the sinuses were taken including a CAT scan, and tracheotomy was performed.

Radiography confirmed that there was a fluid level in the right maxillary antrum. Tomography revealed a haematoma under the orbit (fig. 1) and on December 1, 1982 a Caldwell Luc incision was made for exploration of the antrum. Copious amounts of pus were washed out and a bony defect found in the orbit. A drain was left *in situ*. On December 2, 1982 the patient was breathing spontaneously and, subsequently, made a good recovery. She gave no past history of paranasal sinusitis on subsequent questioning.

Patient 2

A 24-year-old male was admitted on January 18, 1984 with a head injury and required evacuation of a haematoma. After a period of intermittent

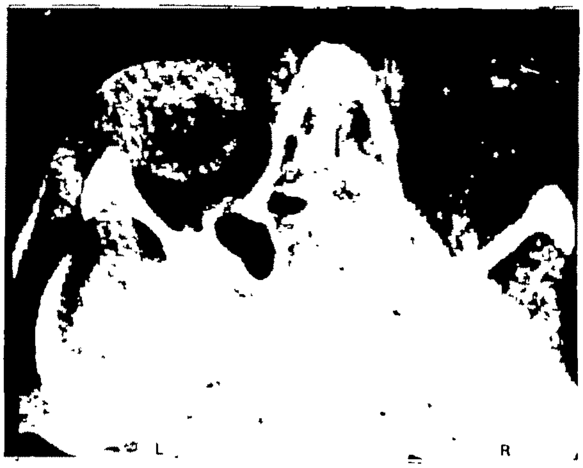

FIG. 1. CAT scan from patient 1.

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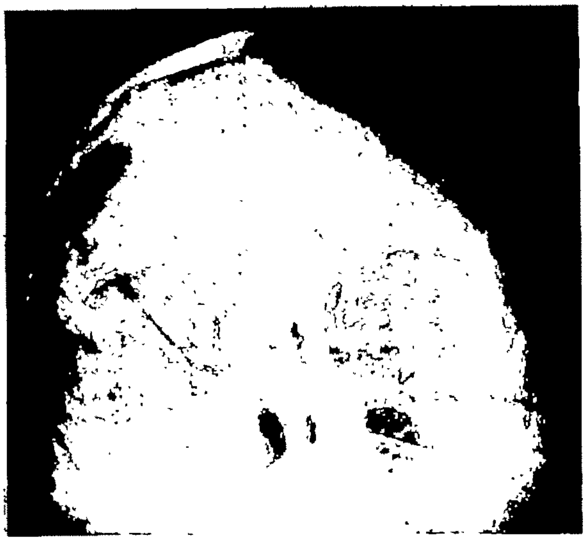

FIG. 2. X-ray of paranasal sinuses of patient 2.

positive pressure ventilation (IPPV) a further evacuation was required and was followed by the insertion of a Ladd intracranial pressure (ICP) monitor. IPPV was continued via a nasal tube because of increases in ICP and a chest infection which followed the aspiration of stomach contents. Whilst still sedated and receiving treatment for the increased ICP, the patient became pyrexial (on January 26, 1984), with some purulent secretions from his tracheal aspirate. No pathogenic organisms were grown from his chest. ICP returned to normal, but a temperature of 39 °C and tachycardia persisted. A gram-negative bacillus was cultured from his blood, but from no other site. All invasive lines were removed, antibiotics were changed and dexamethasone discontinued. A fluctuating fever of 39–40 °C persisted.

Tracheotomy was performed on February 2, 1984. After extubation of the trachea, copious secretions were sucked from the pharynx, and suggested a draining sinus. X-rays (fig. 2) confirmed the diagnosis of right-sided paranasal sinusitis with early eye involvement. At this time right periorbital and conjunctival oedema were present. Antibiotics were continued with addition of Iliadin nose drops. After 2 days the pyrexia resolved. Subsequent enquiry revealed a history of attacks of presumed sinusitis in the past.

DISCUSSION

Prolonged nasotracheal intubation has been used in infants and young children for 20 yr (Allen and Steven, 1965; McDonald and Stocks, 1965). Complications have been reported widely, but concern mainly obstruction of the tracheal tube and the development of subglottic stenosis, both of which may be decreased to an acceptably low level with meticulous attention to detail. Other complications include post-extubation stridor and nasal ulceration. No reports of paranasal sinus infection exist in children, which is perhaps not surprising since, in this age group, the sinuses are poorly developed.

Beamer and Prough (1983) found an incidence of complications of nasotracheal intubation in adults as low as 3%. Complications included epistaxis, sinusitis, nasal necrosis, retropharyngeal lacerations and, in neonates, otitis media.

The recent survey by Pippin, Short and Bowes, (1983) of long-term tracheal intubation in adults suggests that a tracheostomy is most likely to replace a tracheal tube between 7 and 14 days. However, some workers continue nasotracheal intubation for periods of several months (Harrison and Tonkin, 1968; Via-Reque and Rattenborg, 1981). A study of complications and consequences of endotracheal intubation and tracheostomy in 150 critically ill patients by Stauffer, Olsen and Petty (1981) found adverse consequences in 62% of all endotracheal intubations and 66% of all tracheostomies. Paranasal sinusitis was not listed as a complication of endotracheal intubation.

Damage to the nasal septum may be induced during insertion of a nasotracheal tube, ulceration may occur around the nares and, more recently, ulceration of the inferior turbinate has been described in a two-and-a-half year old child (Sherry, 1983). Predisposing factors in this case included major surgery with catabolism and endocarditis.

That the technique of prolonged nasal intubation should restrict drainage from the sinuses is not surprising and it is recorded as a relative contraindication to use of the nasal route (Rie and Wilson, 1983). However, of the many reported complications, infection at this site is unusual. McKenzie (1983) suggested that sinusitis is an important cause of latent pyrexia and O'Reilly and his colleagues (1984) drew attention to its frequency, and the difficulty in making the diagnosis. Sinusitis associated with nasotracheal intubation was thought to account for 5% of nosocomial infections in one critical care unit over a 2-year period (Caplan and Hoyt, 1981). Critically ill patients are very prone to infection. Associated hypotension and poor tissue blood flow will discourage normal bacteriostatic mechanisms and steroid therapy, administered in both our patients, further predisposes to infection. Failure of drainage from the sinuses as a result of pressure from a nasotracheal tube will provide a nidus for blood-borne infection. Cavernous sinus thrombosis is a potential hazard. Subsequent tracheal stenosis is more likely in the presence of infection.

It seems most likely that the infection in these two patients was related to the presence of the nasotracheal tube. A high index of suspicion should be maintained when factors predisposing to infection exist in patients undergoing prolonged nasotracheal intubation. If more of these problems are reported, this will discourage the use of the nasal rather than the oral route for intubation in adults or, if this is unacceptable, earlier tracheotomy may be more appropriate.

(Since this report was written, a further patient has been observed in whom Pa_{O_2} decreased for no apparent reason after removal of the nasotracheal tube. Subsequently, the patient was found to have a purulent right-sided maxillary sinusitis resulting in pulmonary aspiration. After sinus washouts arterial oxygenation improved. Cause and effect cannot be proven, but the improvement after sinus washout is suggestive.)

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Br. J. Anaesth. (1985), 57, 1029–1037

PAROXYSMAL ELECTROENCEPHALOGRAPHIC DISCHARGES DURING ENFLURANE ANAESTHESIA IN PATIENTS WITH A HISTORY OF CEREBRAL CONVULSIONS

M. YAMASHIRO, M. SUMITOMO AND H. FURUYA

SUMMARY

The electroencephalogram (EEG) was monitored through all phases of enflurane anaesthesia in dental outpatients with a history of cerebral convulsions which had been well controlled with anticonvulsant drugs. Abnormal EEG activity which differed from the background activity was observed in three patients. Their case reports are presented.

If general anaesthesia is required for dental outpatients, agents with the fewest side effects and the most rapid recovery should be selected. Enflurane is one of the best drugs for this purpose when one considers its physicochemical properties and its pharmacological characteristics (Virtue et al., 1966; Dobkin et al., 1968; Chase et al., 1971; Ogli and Saki, 1975).

While seizure activity has been reported in association with enflurane, it is considered that a history of cerebral convulsions is not a contraindication to its use (Dukes, 1980).

The present study was undertaken in patients receiving long-term anticonvulsant therapy in whom the incidence of epileptogenic activity was noted during the administration of enflurane.

PATIENTS AND METHODS

We present three patients who underwent dental treatment as outpatients under general anaesthesia. Each had a previous history of cerebral convulsive disorders and had been receiving appropriate anticonvulsant medication regularly; none had shown clinical evidence of convulsions for at least 5 years. In regard to their general health, no other noteworthy tendencies were observed, except for mild mental deficiency. The patients were allowed to continue their regular anticonvulsant treatment until the morning of the operation. Atropine 0.01 mg kg^{-1} was administered i.m. 30 min before the induction of anaesthesia. The EEG was monitored through all phases of anaesthesia. The electrodes were attached to Fp_1, Fp_2 according to the International Ten–Twenty System. The time constant and the high cut were set at 0.3 s and 30 Hz, respectively. Both were connected to a bioelectric amplifier (AB 621 G, Nihon Kohden).

During anaesthesia the EEG and ECG were displayed on an oscilloscope and were stored simultaneously on tape (Elcaset DR. FE-30 Series, Instrumentation Tape Recorder, Sony Magnescale Inc. Tokyo); a permanent record could be obtained, when required. The inspired concentration of enflurane (Engström Emma), and the end-expiratory carbon dioxide concentration (FE_{CO_2}) and the arterial carbon dioxide partial pressure (Pa_{CO_2}) (Normocap, Datex), were monitored.

Anaesthesia was induced with enflurane and sodium thiamylal. Nasotracheal intubation was facilitated by the administration of suxamethonium 1 mg kg^{-1}, and anaesthesia maintained with 1–3% enflurane and nitrous oxide in oxygen.

CASE REPORTS

Patient I

A 16 year-old boy, weighing 54 kg was being treated with phenobarbitone, acetazolamide and carbamazepine. No abnormalities were noted in

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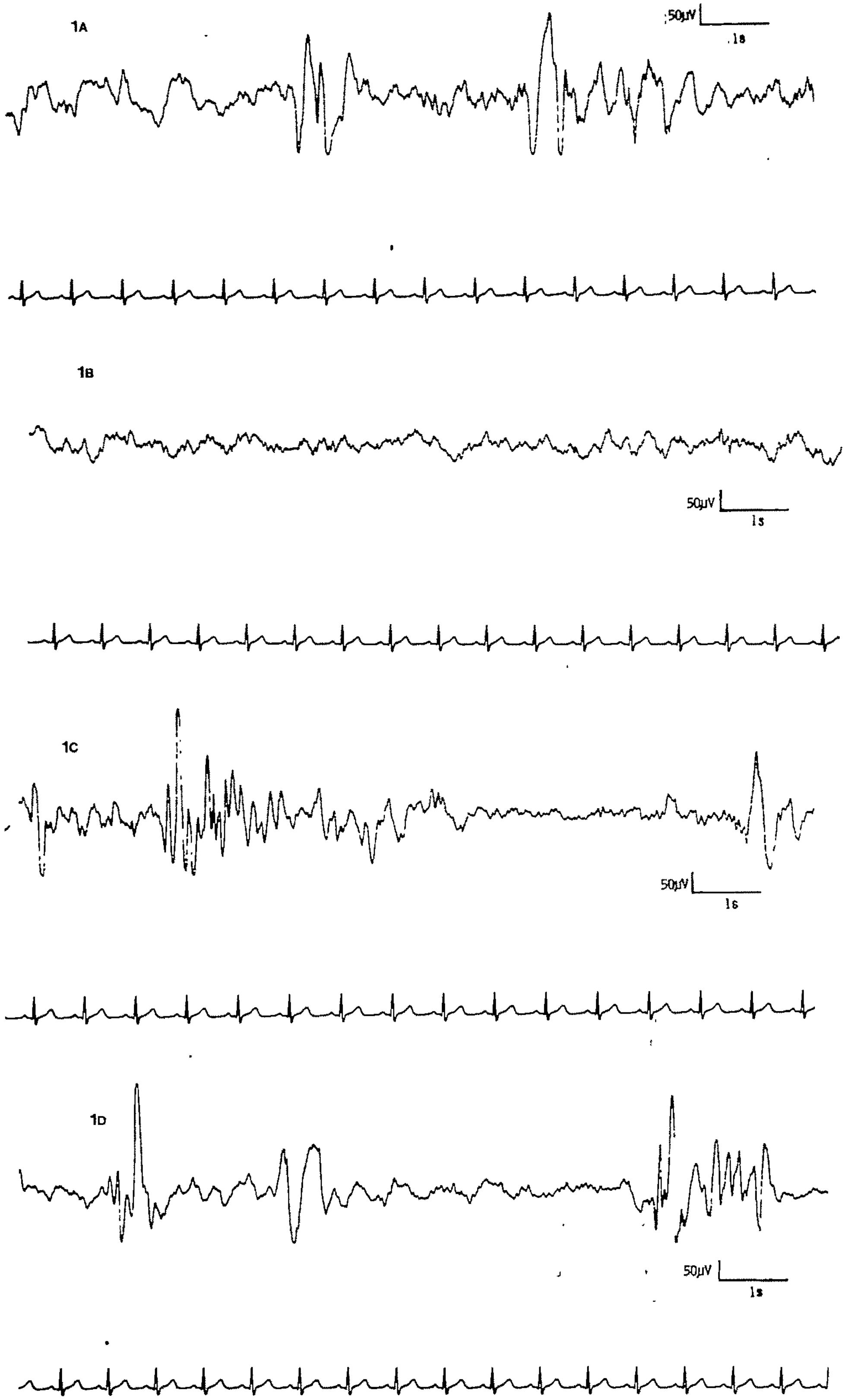
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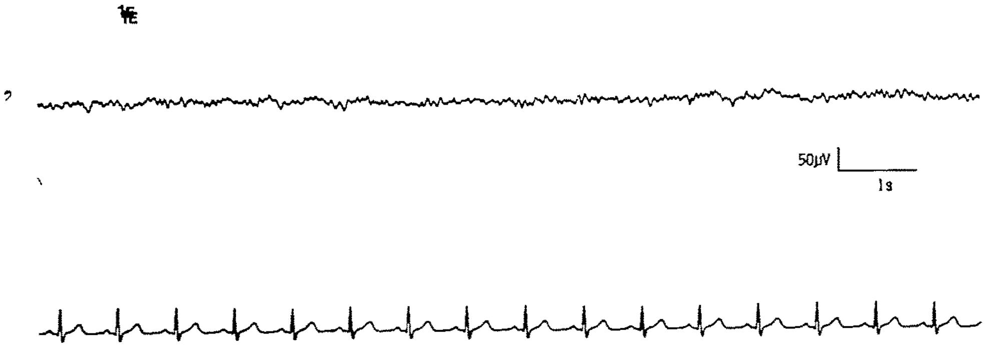


FIG. 1. Patient I. A: Polyspike bursts appeared at intervals of 5–10 s during 2% enflurane and hyperventilation. B: Enflurane 3% and hyperventilation shows an increase in the slow-wave components of the background activity and a lessening of the fast wave components. C: Polyspike bursts appeared when the patient's lungs were hyperventilated and during 1.5% enflurane administration. D: Even during normoventilation under assisted respiration with 1% enflurane, epileptiform activity as shown in the previous figure was observed for a period of approximately 5 min. E: Neither spikes nor high voltage slow waves were observed. Inhalation of 100% oxygen at rest.

the EEG during the induction of anaesthesia with enflurane.

After tracheal intubation, with the inspired enflurane concentration at 2% and at an $F_{\mathrm{E_{CO_2}}}$ of 3.5% ($Pa_{\mathrm{CO_2}}$ 3.5–3.7 kPa), clusters of spikes (fig. 1A) appeared, and continued at 5–10 s intervals. This spike activity disappeared when artificial ventilation was instituted and the $F_{\mathrm{E_{CO_2}}}$ maintained at approximately 5% ($Pa_{\mathrm{CO_2}}$ 5.1–5.6 kPa). Twenty minutes later, in order to maintain the necessary depth of anaesthesia, controlled ventilation was carried out for approximately 5 min. Although the $F_{\mathrm{E_{CO_2}}}$ was 3.5%, no abnormal findings were recorded, with the exception of those for the EEG which were characteristic of 3% enflurane (Neigh, Garman and Harp, 1971) (fig. 1B). For approximately 20 min subsequent to normoventilation with 1.5% enflurane, no abnormalities were observed. However, bursts of spike activity appeared when the patient was, once again, hyperventilated (fig. 1C). When this occurred normocapnia was maintained (1% enflurane); however, the paroxysmal activity (fig. 1D) persisted for about 5 min. The EEG observed during inhalation of 100% oxygen, after all other procedures were finished, contained neither high voltage slow waves nor spikes (fig 1E).

Patient II

The patient was a 14 year-old boy who weighed 34 kg. He had a history of Lennox syndrome as an infant. Since that time, he had been taking anticonvulsant drugs regularly. When he presented, he was taking clonazepan by mouth.

Anaesthesia was commenced using 0.5% enflurane for 3–5 breaths. The enflurane concentration was then gradually increased to 4% by 5 min.

Since the patient had received 4% enflurane for approximately 1 min only, there was no decrease in arterial pressure. Anaesthesia was then maintained with 1% enflurane.

No abnormalities were noted in the EEG before induction (fig. 2A). During induction (1–3% enflurane), when respiration was assisted intermittently to maintain normocapnia, neither spikes nor high voltage slow waves were observed. Figure 2B shows the EEG during induction with 2% enflurane. However, when 4% enflurane was inhaled during induction, bursts of high voltage spike activity and sharp waves appeared superimposed on a background of low amplitude activity (fig 2C). Diazepam 5 mg was injected i.v., suxamethonium 1 mg kg^{-1} administered and the trachea intubated. During intubation, 3 min after the administration of diazepam the EEG revealed high voltage spike and wave complexes (fig. 2D). These complexes began to decrease 5 min after the injection of diazepam. Paroxysmal activity was completely absent during the maintenance of anaesthesia (normocapnia with assisted ventilation) and the administration of 1% enflurane (fig. 2E). Thereafter, no abnormalities were noted on the EEG until the end of anaesthesia. The EEG during inhalation of 100% oxygen after extubation is shown in figure 2F.

Patient III

A 7 year-old girl, weighing 19.5 kg, was receiving sodium dipropylacetate and clonazepam.

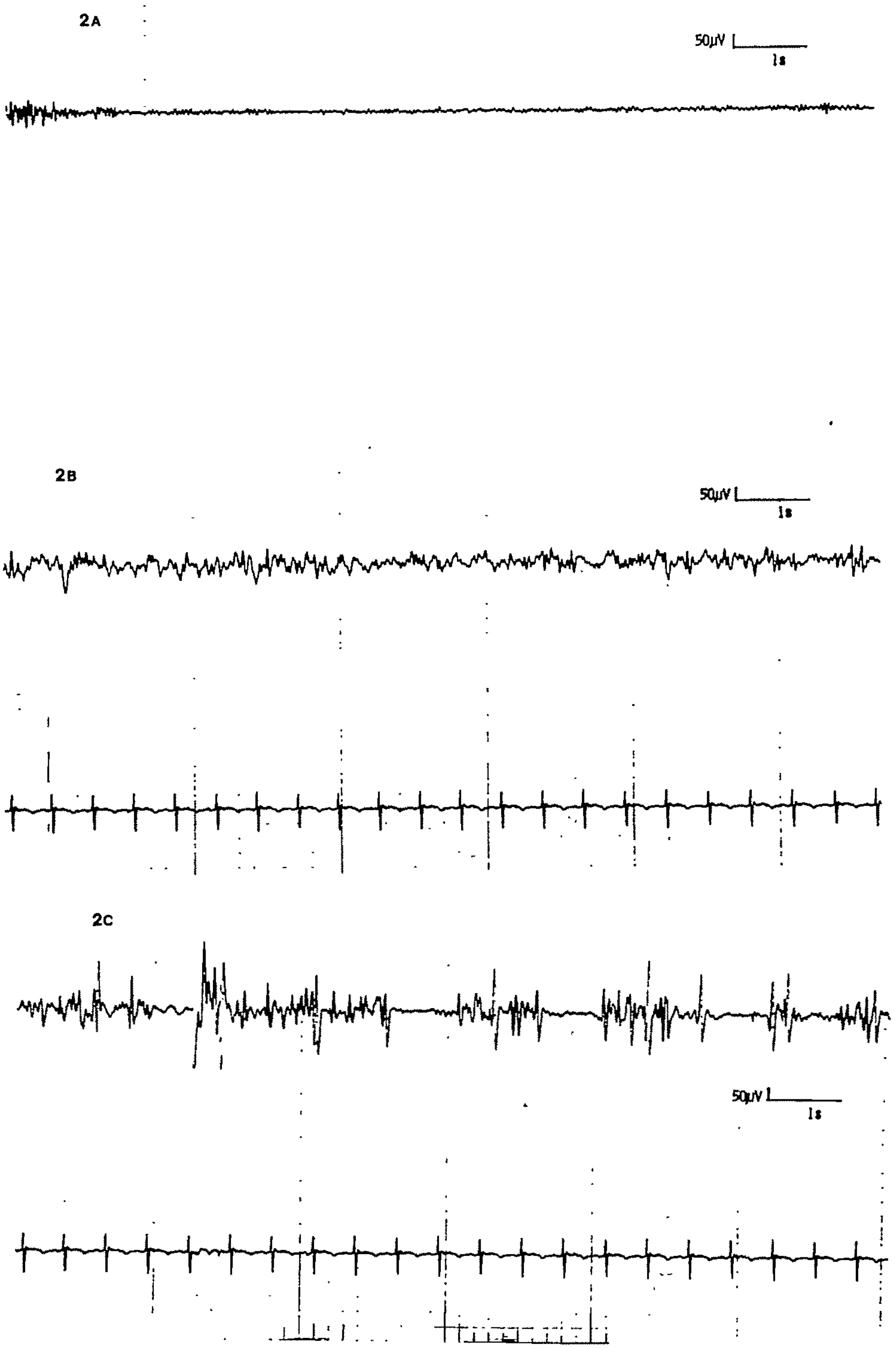
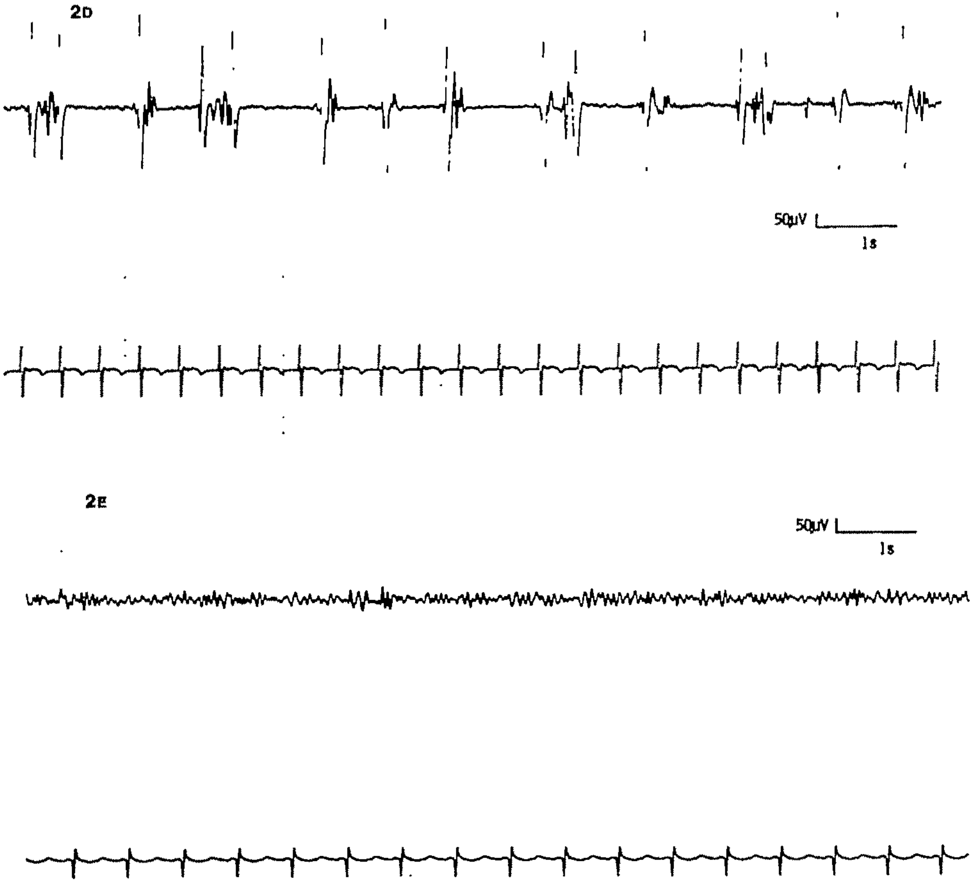
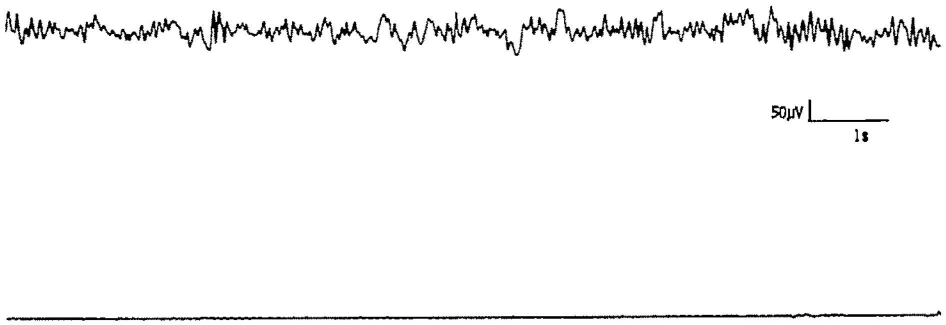


FIG. 2. Patient II. A: During induction with administration of 100% oxygen. No abnormalities were observed at rest while awake. B: An increased frequency of the basic activity but no epileptiform activity was observed in patient II during induction with 2% enflurane and assisted respiration. C: Bursts of high voltage polyspikes and sharp waves superimposed on a low amplitude background activity were observed during induction with 4% enflurane and assisted respiration. D: During tracheal intubation,

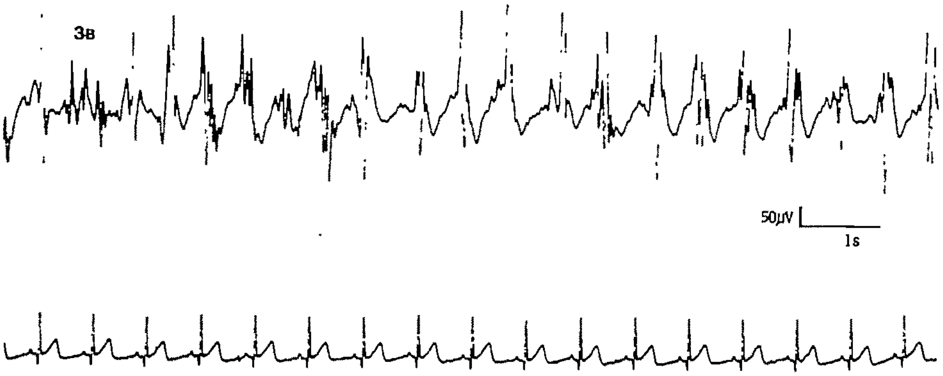


when the blood concentration of diazepam was probably at a peak (3 min after i.v. administration) the epileptiform discharge had not disappeared. E: The epileptiform discharge disappeared completely 10 min after diazepam administration with 1% inspired enflurane and normocapnia. F: After extubation and under 100% oxygen. No EEG abnormalities were noted.

3A



3B



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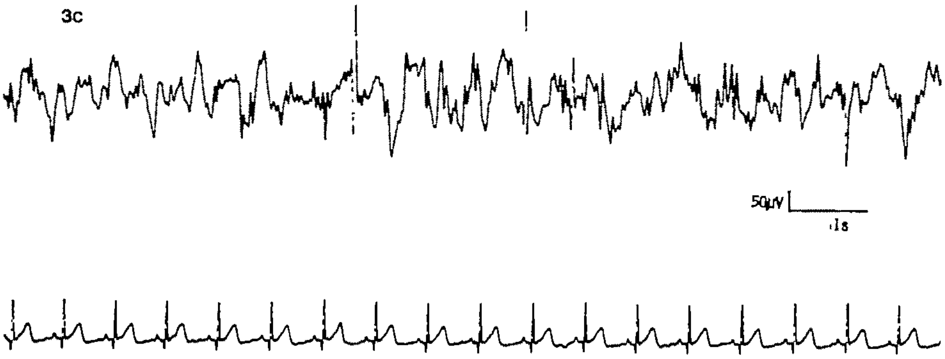
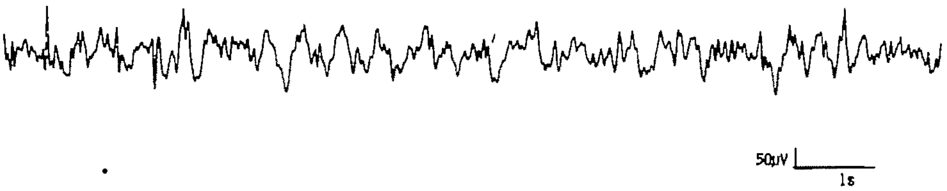


3D



The induction of anaesthesia was performed with sodium thiamylal in combination with enflurane. During the inhalation of 3% enflurane at the time of induction, a characteristic EEG pattern for 2MAC enflurane (Neigh, Garman and Harp, 1971) was observed (fig. 3A). When 2% enflurane was inhaled after tracheal intubation and a state of hyperventilation developed, multiple spike and wave complexes appeared (fig. 3B). These disappeared during the maintenance of normocapnia (assisted ventilation) and the administration of 1% enflurane. Thereafter, bursts of high voltage slow wave activity appeared during the inhalation of 3% enflurane as a result of the decrease in Pa_{CO_2} (fig. 3C). The spikes and high voltage slow waves persisted for a few minutes, even after the inhalation of enflurane was discontinued. Figure 3D shows the EEG during inhalation of 100% oxygen following extubation of the trachea.

DISCUSSION

Enflurane has minimal effects on hepatic function, renal function and the metabolic system, its rate of biotransformation is less than that of other inhalation anaesthetics, and recovery is rapid. These factors render it suitable for general anaesthesia in outpatients. However, the possibility of seizure activity remains a problem. Muscle movement is observed frequently during enflurane anaesthesia. Julien and Kavan (1972) reported epileptoid bursts on the EEG with deeper anaesthesia, and a decrease in Pa_{CO_2} may accelerate enflurane-induced seizure activity (Bart, Homi and Linde, 1971). Furthermore, Darimont and Jenkins (1977) stated that barbiturates, typical anticonvulsants, intensified such enflurane-induced seizure activity.

These data suggest that the use of enflurane in high concentrations, when the Pa_{CO_2} is decreased, or when it is used in combination with a barbiturate, increases the probability of the induction of seizures.

On the other hand, Mori (1980) and Urabe (1981) reported that enflurane has an anticonvulsive effect in the cat experimental seizure model, at low and high concentrations. Gallagher, Galindo and Richey (1978) observed the disappearance of seizure activity noted during anaesthesia by the inhalation of enflurane at a high concentration (4%). Opitz and Oberwetter (1979) reported that they were able to give enflurane safely, even to epileptic patients. Thus, at the present time, enflurane is not generally considered to be contraindicated in patients with a history of cerebral convulsive disorders (Dukes, 1980).

In the three cases presented in this paper, the fact that no convulsions had occurred for at least 5 years, suggested that control was adequate. Following the precedent of Opitz and Oberwetter (1979), we permitted the oral administration of anticonvulsants until the morning of the day when anaesthesia was given. A previous report (Bart, Homi and Linde, 1971) which noted that the seizure activity associated with enflurane was enhanced by hypocapnia, was confirmed by our observations. The spikes, polyspikes, spike and wave complexes and high voltage slow waves which appeared in the EEG in the present cases, and which differed from background activity, resembled those attributable to epilepsy. It has been suggested that, when the enflurane concentration is less than 1.5 MAC (about 2.5%) and hypocapnia is avoided, the occurrence of seizures can be minimized (Michenfelder and Cucchiara, 1974). However, even when the inhalation concentration of enflurane was 1.5% or 2%, we recognized paroxysmal discharges in the EEG.

In the first patient, once clusters of spikes had appeared, they did not disappear for a few minutes even though normocapnia was maintained by assisted respiration and the enflurane concentration was only 1%. Therefore, enflurane may induce paroxysmal discharges during normocapnia and at a concentration commonly considered not to induce seizures.

In the second patient, polyspike and sharp waves superimposed on low amplitude background activity appeared suddenly during induction when 4% enflurane was being administered. In patients with mental deficiency or severe anxiety, the establishment and maintenance of the i.v. route

FIG. 3. Patient III. A: During induction with 3% enflurane and assisted ventilation the characteristic EEG of approximately 2 MAC enflurane was obtained with slightly high amplitude 7–12-Hz waves. B: Polyspike and wave complexes appeared during 2% enflurane administration and hyperventilation. C: With a decrease in Pa_{CO_2}, spikes and high voltage slow waves appeared during 3% enflurane administration and hyperventilation. D: After extubation and under 100% oxygen administration, high voltage slow waves predominate, but no polyspikes or polyspike and wave complexes can be recognized.

before anaesthesia induction is often difficult. Therefore, while it is believed that 4% enflurane may involve a greater possibility of seizure induction, as high a concentration as permissible should be used to complete induction quickly in such patients.

Gallagher, Galindo and Richey (1978) and Mori (1980) stated that a concentration of 4% was not necessarily dangerous. However, when enflurane is administered to patients with a history of cerebral convulsive disorders, burst of paroxysmal activity may occur, even when anticonvulsants are administered and inhalation is carried out using a low concentration. In the second patient, the polyspike activity which appeared during the induction of anaesthesia had not disappeared 3 min after diazepam 5 mg i.v. during intubation, when the blood concentration of diazepam was considered to have reached its peak. During the administration of 1% enflurane and the maintenance of normocapnia with assisted ventilation, the clusters of spikes disappeared about 8 min after the commencement of the injection of diazepam. Abnormal findings, for example spike or sharp-wave bursts in the EEG observed in patients with epilepsy ordinarily disappear immediately after an i.v. injection of diazepam 2.5–8 mg and the basic activity becomes rhythmical or fast (Murata, 1969). Since this patient had been receiving an anticonvulsant of the same benzodiazepine class over a long period of time, it is possible that he had a greater tolerance to diazepam, with the result that the dose was insufficient.

Although it has been reported that the combined use of barbiturates and enflurane intensifies enflurane-induced seizures (Darimont and Jenkins, 1977), our experience revealed that, in some patients, the EEG was more stable than it was before the induction of anaesthesia. In the third patient, on the other hand, when 3% enflurane was administered during induction, EEG findings consisted mainly of slow waves mingled with spikes. These are considered to be the EEG characteristics of approximately 2 MAC enflurane (Neigh, Garman and Harp, 1971). The injection of sodium thiamylal 100 mg i.v. did not produce any marked changes in the EEG. The combined use of the barbiturate and enflurane did not appear to intensify enflurane-induced paroxysmal activity in any of these patients.

Actual convulsions or twitching of the limbs were not observed in these three patients. However, clusters of spikes, spike and wave complexes and high voltage slow wave bursts which appeared in the EEG during the course of anaesthesia resembled those observed during epileptic attacks (Shimazono, Kitamura and Ōtomo, 1976). Therefore, the possibility exists that when such paroxysmal discharges are noted, convulsions may develop with a resultant increase in cerebral oxygen consumption.

Enflurane was administered to patients with a history of cerebral convulsive disorders who had been examined regularly by specialists, treated with anticonvulsants for long periods, and in whom no abnormalities were found in the EEG before anaesthesia. However, abnormal EEG findings differing clearly from background activity were recognized during anaesthesia.

Based on our experience, we suggest that anaesthetics without epileptogenic properties be used in patients with a history of cerebral convulsions, in order to avoid the possibility of producing overt seizures during anaesthesia.

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Br. J. Anaesth. (1985), **57**, 1038–1046

CORRESPONDENCE

LABORATORY DIAGNOSIS OF MALIGNANT HYPERPYREXIA SUSCEPTIBILITY (MHS)

Sir,—Confirmation of clinical diagnosis of malignant hyperpyrexia (MH) and the subsequent family investigation of relatives of MH patients depends at present on a laboratory study of living muscle tissue. Until recently, each laboratory has determined its own limits of normality from control data which are difficult to obtain. The European MH Group encouraged all member departments to adopt the same experiment procedure, enabling a more rapid collection of comparable data than any individual department could have achieved in the same time.

The paper reporting the new diagnostic criteria (European MH Group, 1984) described three categories of patient, namely MHS (patients undoubtedly susceptible to MH), MHN (patients undoubtedly not susceptible to MH) and MHE, whose laboratory results were equivocal according to the new criteria.

The laboratory test limits were purposely set to restrict the diagnosis of MHS and MHN to those patients whose laboratory results would be universally acceptable; both of these diagnoses are of great clinical importance and potential danger. An extended MHE group provided a degree of security for the patients because it was agreed that most of these patients would be reported as MH susceptible in the clinical context.

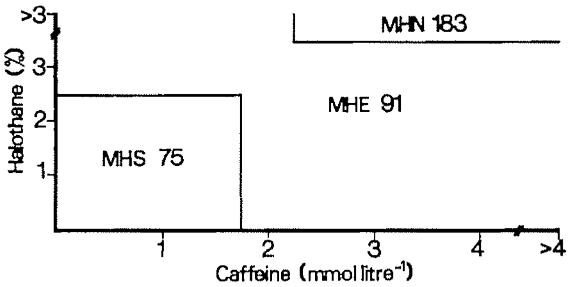

FIG. 1. Diagnostic grouping of 349 patients according to original criteria.

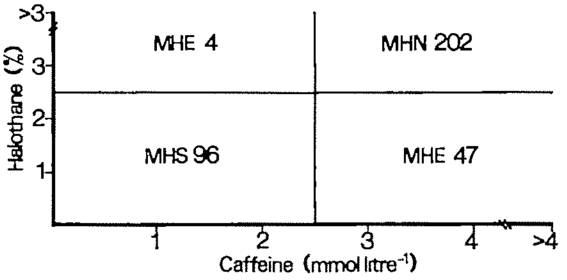

FIG. 2. Re-grouping of the 349 patients according to new diagnostic limits.

Whilst the fundamental importance of the MHE category was recognized when the protocol was published (Ellis, 1984), it was stated than that this category would be subject to "permanent review", and would be reduced in proportion in the light of experience. If the inheritance of MH is accepted as a dominant characteristic, there should be no equivocal MHE category, as heterozygotes would be identified as MHS and homozygote normals as MHN. The MHE result must represent a "grey area" of diagnosis which has no genetic relevance.

Combining results obtained by member units of the European MH Group since the acceptance of the protocol, 349 patients were diagnostically grouped as follows: 75 (22%) as MHS; 183 (52%) as MHN; 91 (26%) as MHE (fig. 1).

Following a review of all 91 MHE patients, and comparing the laboratory result with the case material and the family relationships, it was agreed to adjust the diagnostic limits to those shown in figure 2, namely:

MHS: a halothane contracture at 2% v/v or less AND a caffeine contracture at 2 mmol litre^{-1} or less;

MHN: no halothane contracture at 2% v/v or less AND no caffeine contracture at 2 mmol litre^{-1} or less;

MHE: all other results.

This revision can be seen, first, to have rationalized the diagnostic limits between the three categories and, second, to have almost halved the MHE group from 91 to 51 patients (15%). Of the 40 patients removed from the MHE group, 21 have been incorporated into the MHS group, and 19 into the MHN group. It is still envisaged that many of the MHE patients should be accepted as clinically susceptible to MH, pending further elucidation.

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DURATION OF FAST BEFORE ELECTIVE SURGERY

Sir,—Miller, Wishart and Nimmo (1983) reported that consumption of a light breakfast was not contraindicated before surgery and general anaesthesia in light of their findings of no difference between the volume or pH of gastric contents in a fed population compared with a fasted population. In their conclusion they imply that a pH of 3.0 is safe when discussing aspiration of gastric contents.

We believe that aspiration of food particles is hazardous even when the pH is >2.5. Wynne and associates (1979) demonstrated that the aspiration of particulate gastric contents at a pH of 4.3 was associated with severe lung injury. Moran (1951) found the pathological changes caused by non-acidic ground food aspiration in the guineapig to be identical to food aspiration pneumonia in man. Schwartz and co-workers (1980) add further support to this contention by demonstrating that aspiration of gastric contents with a pH of 5.9 was associated with changes consistent with pneumonitis. These findings on particulate matter may contradict the classic findings on Mendelson's syndrome (Mendelson, 1946).

Miller's study does not examine the effect of a light breakfast on the amount of particulate matter in the stomach. The discomfort involved in fasting seems insignificant compared with the risks incurred by aspiration of foods.

Aspiration of particulate matter clearly can be associated with severe morbidity and should be avoided. We therefore encourage the continued practice of fasting patients for at least 4 h before elective surgery.

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Sir,—Thank you for allowing me to comment on the letter from Drs Goldberg and Sosis. Although I do not wish to reply specifically to the points raised in their letter, I would take issue with the last sentence of their first paragraph. I would point out to your readers that we did not imply that a pH of 3.0 is safe when one is discussing aspiration of gastric contents.

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PARACETAMOL KINETICS AND GASTRIC EMPTYING

Sir,—We are investigating immediate post-partum gastric function and the influence of metoclopramide on it, using paracetamol absorption kinetics as a measure of gastric emptying (Heading et al., 1973, Clements et al., 1978; Nimmo, 1978). Murphy and colleagues (1984) describe the effects of metoclopramide on gastric emptying in pregnant patients also using paracetamol absorption as a marker. Their application of this useful method is, however, suspect.

Nimmo and colleagues (1975) demonstrated a correlation coefficient of 0.94 between the amount of paracetamol absorbed over 1 h (i.e. area under the plasma concentration curve after 1 h) and gastric emptying. A single sample at a fixed time, as used by Murphy and colleagues (1984) cannot be an accurate reflection of the amount absorbed, as one has no knowledge of curve profiles. Rapid absorption (or emptying) could result in a sampling during the downstroke of the curve and slow absorption (or emptying) during the upstroke. Comparisons of results obtained by single "spot" sampling are therefore invalid.

The influence of metoclopramide on gastric emptying in the presence of opioids remains unclear and deserves further study.

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Sir,—Thank you for allowing us the opportunity to reply to Drs Finnegan and Jyn who take issue with the methodolology used in our study of gastric emptying in pregnant patients.

In the original work, Heading and colleagues (1973) related the rate of gastric emptying, as measured by a sequential scintiscanning technique, to paracetomol absorption. In all cases, peak plasma paracetamol concentrations are quoted and not "area under curve" (AUC) estimations. These results showed that "there were (also) statistically significant correlations between the half-time of gastric emptying and the plasma concentration at 30 min and at 60 min." All subsequent studies by these authors (Nimmo et al., 1973; Nimmo, Wilson and Prescott, 1975; Nimmo et al., 1975; Nimmo, 1978; Wilson, 1978) quote mean peak plasma concentrations in their results. There is one reference to plasma concentration–time, area under curve estimation (figure 4, Nimmo et al., 1975) and it is assumed that it is in reference to this that Drs Finnegan and Jyn believe AUC estimations should be used.

For our study, we accepted the validity of the "paracetamol absorption" technique and used mean peak plasma paracetamol concentrations as an indirect index of the rate of gastric emptying. We do not, therefore, accept that the methodology used is invalid. It is possible that AUC estimations might be a better method of analysis, but would certainly be more difficult to undertake and control in labouring patients. In any event, it is our opinion that the plasma paracetamol concentrations in our study were of such magnitude in the different subgroups as to withstand statistical evaluation by either method of assessment.

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ORAL RANITIDINE IN LABOUR

Sir,—Despite many improvements in obstetric anaesthesia, the inhalation of gastric contents remains an important cause of maternal mortality. Experimental work in animals (Mendelson, 1946; Teabeaut, 1952) suggests that Mendelson's syndrome is likely to occur when the pH of the inhaled material is below 2.5 and it is probable that the inhalation of a volume as small as 25 ml (Roberts and Shirley, 1974) may be fatal. The H_2-receptor antagonists appear an attractive method of increasing gastric pH. Ranitidine, because of its different chemical structure, appears to have less side-effects than cimetidine and has a longer duration of action. The purpose of this study was to determine whether the administration of ranitidine 150 mg by mouth at 8-hourly intervals to patients in induced labour would reliably increase gastric pH to a safe value.

Nine healthy patients receiving no medication and with no history of peptic ulceration before pregnancy were studied. All gave informed consent. All were admitted to hospital on the evening before the surgical induction of labour. At 22.00 h on the evening of admission, ranitidine 150 mg was given by mouth. Thereafter the same dose was given 8-hourly until delivery. Just before the induction of labour next morning, a size 8-French gauge nasogastric tube was passed. Five millilitre of gastric contents was aspirated. This was repeated every 2 h until the second stage of labour was reached. The patient's stomach was then emptied as far as possible, using the nasogastric tube, before delivery and the final volume of aspirate was measured. The pH of all samples of gastric aspirate was measured using a Corning EEL model 7 pH meter. Apgar scores were noted at 1 and 5 min after delivery. The babies were observed closely for 48 h after delivery for any feeding or respiratory difficulties. Samples of maternal and cord blood were taken just after delivery, and the plasma concentrations of ranitidine measured.

When the serial pH values for each of the nine patients were reviewed (table I) it was noted that one patient (No. 5) had an unacceptably low pH value (below 3.0) at induction and in early labour but an acceptable pH value (4.8) at delivery. Several other unacceptably low pH values were obtained. One of these was at delivery (patient No. 9). These low pH values all occurred 1 h before or after ranitidine administration. Mean pH measurements (i.e. the mean of all the pH values taken at one time) were consistently at their highest 5 h after ranitidine administration and thereafter decreased until subsequent doses became effective (fig. 1). Gastric volumes ranged from 20 to 45 ml (mean 30 ml). The mean Apgar scores at 1 and 5 min were 9 and 10, respectivly. No baby developed respiratory or feeding difficulties or jaundice. Maternal and fetal cord plasma ranitidine concentrations showed a wide variation (36–430 ng ml^{-1} and 40–260 ng ml^{-1} respectively). The mean fetal: maternal ratio of plasma ranitidine was 0.7, showing that ranitidine crosses the placenta in significant amounts. Five of the patients

TABLE I. *Table of serial gastric pH values in nine patients during labour. R = ranitidine given. Values < 3 are in bold type*

Patient No.	Time											
	9.00		11.00	13.00	R	15.00	17.00	19.00	21.00	R	23.00	01.00
1		6.3	6.5	7.7		6.5						
2	5.1		6.0	**2.2**		5.8	7.1	7.0	5.3			
3	6.1		5.6	7.0								
4	4.6		5.8	5.8		4.1	4.1	6.6	3.4		5.9	
5	**2.1**		**2.8**	4.8								
6		5.7	5.9	4.8		**2.8**	3.3	5.3	4.6		3.0	
7	6.0		5.6	5.8		5.2	5.6	5.6	4.9		5.9	6.2
8	6.9		6.9	3.5								
9	5.1		5.9	5.6		6.0	6.3	6.3	3.3		**2.7**	
No.	7		9	9		6	5	5	5		4	
Mean	5.13		5.67	5.24		5.07	5.28	6.16	4.30		4.38	
SEM	0.58		0.39	0.56		0.56	0.70	0.31	0.40		0.88	

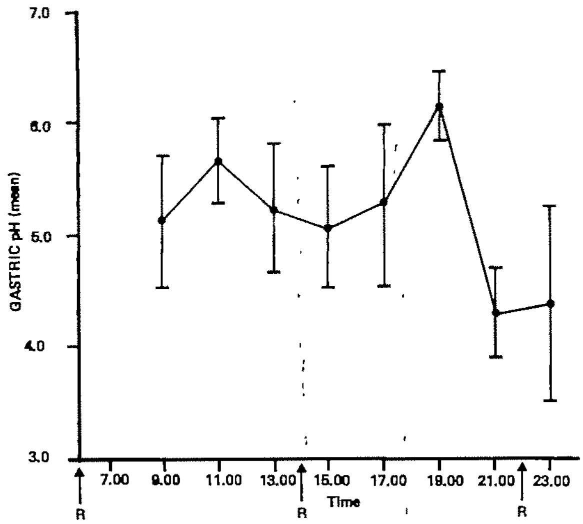

FIG. 1. Mean gastric pH values in relation to administration of ranitidine 150 mg (R). Bars represent SEM.

were delivered by Caesarean section (four under extradural anaesthesia alone). Blood loss at delivery was within normal limits in all cases.

From the results several points are worth noting. Of the nine patients, seven had extradural analgesia and two received pethidine 150 mg i.m. (patients No. 2 and 4; both 6 h after induction). It might have been expected that, following pethidine administration, absorption of ranitidine would have been slowed and the gastric volumes in these patients at delivery greater (McAuley et al., 1984). However, in both these patients gastric pH values after pethidine were acceptable (table I) and gastric volumes (45 and 20 ml) at delivery similar to those of the other patients.

Pharmacokinetic studies in man show that plasma ranitidine concentrations of greater than 100 ng ml^{-1} (Peden et al., 1979) are required to halve the secretion of gastric acid. Three of the patients had plasma concentrations below this at delivery, although in only one (patient No. 9) was this accompanied by a low gastric pH. These three patients all delivered 1 h before or after administration of ranitidine. It is probable that there is a delay before a decrease in plasma ranitidine concentration shows itself by a decrease in gastric pH.

The mean gastric volume at delivery of 30 ml confirms that antacid therapy with ranitidine does not decrease the volume of gastric contents to an insignificant level. However, the gastric volumes found in this study were considerably lower than most of those found in two other studies using ranitidine in labour (Gillett, Watson and Langford, 1984; McAuley et al., 1984). An explanation could be that the patients in this study received two doses of ranitidine before the induction of labour was carried out. All patients were fasted from 07.00 on the day of induction.

Of the five patients delivered by Caesarean section, four were judged by the obstetricians likely to require operative delivery before induction. The administration of ranitidine is unlikely to have been of significance.

In conclusion, we feel that the results obtained from studying nine patients made it unsafe to continue with this antacid regimen. As most of the unacceptably low pH values occurred 1 h before or 1 h after ranitidine administration, and as peak mean pH values always occurred 5 h after ranitidine administration, it is probable that more frequent administration of ranitidine would be successful in maintaining gastric pH at a satisfactory value. Two recently reported studies (Gillett, Watson and Langford, 1984; McAuley et al., 1984) have shown that ranitidine 6-hourly by mouth in labour gives more satisfactory results.

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SAFE ANAESTHETIC FOR LAPAROSCOPY WITH SPONTANEOUS RESPIRATION

Sir,—We had read with great interest the article of Drs Kurer and Welch (1984) and were disappointed with their choice of halothane as an anaesthetic for laparoscopy in the group of patients with spontaneous respiration. According to the studies of Desmond and Gordon (1970), Hodgson, McCleland and Newton (1970) and Scott and Julian (1972), it was shown that, during laparoscopy with spontaneous respiration, halothane depresses ventilation, particularly tidal volume and, in direct relationship to the hypercapnoea, the frequency of arrhythmias increases. Why not use a reliable, simple anaesthetic technique for laparoscopy under spontaneous ventilation?

During recent years we have use a modified technique of Shane (1983) which includes "conscious sedation" and local anaesthesia. Patients are premedicated with hydroxyzine 1.5 mg kg^{-1} i.m. 1 h before the procedure. A full explanation of all stages of the laparoscopy is given. When the patient is positioned in the lithotomy position on the operating table with 15–30° head-down tilt, fentanyl 1 μg kg^{-1} and flunitrazepam 0.01 mg kg^{-1} are given i.v., followed in 5 min by local anaesthesia of the skin. When the laparoscope reaches the peritoneal cavity, a bolus of 1% lignocaine 1.5 mg kg^{-1} is instilled. All patients received oxygen 4 litre min^{-1} via Venturi mask. In a controlled study (unpublished data) with 30 women we monitored ECG, arterial pressure (Dinamap 845), end-tidal carbon dioxide and arterial blood-gas tensions. The results showed slight but insignificant increase in end-tidal carbon dioxide which was confirmed with insignificant increase in

Pa_{CO_2} and pH. There were also small increases in mean arterial pressure and heart rate. In all patients the measured values returned to the control figures within 10–15 min of deflation of the peritoneal cavity. No obvious changes were noted in the ECG. All patients were responsive to commands during laparoscopy and fully awake and calm at the end. Interviewed 2–3 days after the procedure all patients noted their desire to have the same technique if a further such investigation was required. "Conscious sedation" with local anaesthesia appears to be a safe and simple alternative anaesthetic method for laparoscopy in certain patients when for any reason general anaesthesia is undesirable.

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Sir,—Thank you for the opportunity to reply to the letter from Drs Beilin and Vatashsky in which they question the use of halothane in the spontaneously breathing group of patients described in our article. Our study was an evaluation of two techniques used for many years to the satisfaction of anaesthethists and surgeons at the Royal Berkshire Hospital. We did not attempt to select or modify the anaesthetic techniques already in current use and we were not investigating the advantages or disadvantages of individual anaesthetic agents. We believe that we were primarily concerned with the evaluation of the efficacy and the associated morbidity of allowing patients to breathe spontaneously against the more accepted technique of intubation and artificial ventilation.

Concerning the use of halothane itself, as is evident from our study, we were not able to demonstrate a significant difference between carbon dioxide tensions between the two techniques or, indeed, an unacceptably high end-tidal $P\mathrm{CO}_2$ concentration in the spontaneously breathing group. I appreciate that the publications quoted are always used when discussing this topic, but we believed that in our study the considerable reduction in Trendelenburg tilt, the decreased insufflation volumes, the shorter duration of the procedure and the increased familiarity of the surgeons with this procedure since those studies were performed, contribute to our different findings and, as a consequence, there was no contraindication to the use of halothane.

I am not familiar with the technique of "conscious sedation" for gynaecological laparoscopy described by Drs Beilin and Vatashsky, and am not aware that it has been described in the British literature. However, I understand that a similar procedure is available at a few centres in the U.K. with the emphasis on local anaesthesia, rather than sedation. The patients are well motivated, carefully councilled and frequently turned down if they are considered overweight, or have a previous history that might suggest the presence of intra-abdominal adhesions. No i.m. premedication is used, as is the usual practice for day-case procedures, and only tubal ligation laparoscopies are performed using this particular anaesthetic technique. It is encouraging that Drs Beilin and Vatashsky found 100% acceptance by the patients at interview 2–3 days following their procedure. Though the authors do not give values of end-tidal $P\mathrm{CO}_2$ concentration, it would be interesting to know whether they are significantly less than the values we obtained in our study. Perhaps for day-case surgery this type of approach should be evaluated more closely, and less reliance placed on general anaesthetic techniques.

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EXCRETION OF LORAZEPAM INTO BREAST MILK

Sir,—The excretion of sedative drugs into breast milk is an important consideration should anaesthesia and surgery be necessary during the post-partum period in the mother who is breast feeding. It is known that some benzodiazepines and their metabolites are found in the milk of a nursing mother (Brandt, 1976) and that these may result in neonatal lethargy, weight loss and electroencephalographic changes characteristic of sedative medication (Patrick, Tilstone and Reavey, 1972). In addition, diazepam has been detected in the serum and urine of an infant being breast fed by a mother taking oral diazepam (Erkkola and Kanton, 1972).

Lorazepam, by mouth, is now established as an effective agent for premedication in many areas of anaesthesia. Its transfer across the placenta has been studied in women in labour (McBride et al., 1979). The ratio of neonatal to maternal plasma lorazepam concentrations at delivery in women undergoing routine surgical induction of labour ranged from 0.85 to 1.33. At doses of 2.5 mg i.v., the drug had no effect on the 1- and 5-min Apgar scores. Anecdotal data (Whitelaw, Cummings and McFadyen, 1981) would suggest minimal excretion of lorazepam into breast milk.

There is a need to define suitable anxiolytic and sedative drugs for administration to the breast feeding mother. The two cited studies (McBride et al., 1979; Whitelaw, Cummings and McFadyen, 1981) suggest lorazepam might fulfil these requirements. To confirm this, we studied the drug as premedication in four breast feeding mothers scheduled for post-partum sterilization.

All the women, each weighing more than 55 kg, were premedicated with lorazepam 3.5 mg orally 2 h before surgery. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained with nitrous oxide, oxygen and fentanyl. Alcuronium was used to achieve neuromuscular blockade. Four hours after premedication, a 10-ml sample of breast milk was expressed by the mother and simultaneously a 10-ml sample of venous blood was taken. Analysis for free lorazepam concentrations was performed using electron capture gas chromatography following extraction of the samples into ethyl acetate. The results are shown in table I.

These results indicate the low passage of drug into breast milk. The free drug concentrations measured in the expressed milk (8 and 9 ng ml^{-1}) and, therefore, the amount available to the newborn are significantly lower than those reported in the new born by McBride and his colleagues (23–82 ng ml^{-1}).

TABLE I. *Free lorazepam concentrations (ng ml^{-1})*

Plasma	Milk	% Plasma concentration
38	9	23.7
54	8	14.8
35	9	25.7
35	8	22.9

There appears to be no published correlation between plasma drug concentrations and dynamic effects (such as drowsiness). However, McBride and co-workers concluded that maternal concentrations of 30–40 ng ml^{-1}, although providing adequate anxiolysis, did not have a pronounced soporific effect upon the mother, nor did they have any effect on the neuro–behavioural responses of the new born.

We would therefore conclude that oral premedication with lorazepam in breast feeding mothers would appear to be safe.

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FIXATION OF EXTRADURAL CATHETERS

Sir,—Fixation of extradural catheters by subcutaneous tunnelling (Carl, Crawford and Ravlo, 1984) is a satisfactory method which I have also used.

I have developed a simple modification that makes this method easier and quicker. The tunnelling is performed using a 15-cm long 16-gauge (Longdwel B-D) intravenous cannula. The cannula (plus needle) is inserted through the skin, after a weal is raised 15 cm lateral to the insertion site (incision in the midline should be made before the extradural catheterization); local anaesthesia of the tunnel is performed while the cannula is advanced under the skin, a syringe filled with local anaesthetic being attached to the needle. Once the insertion site is reached, the needle is withdrawn and an extradural catheter is passed through the cannula—which is removed at the end of the procedure. This procedure is repeated until the desired site is reached. With this modification the length of the tunnel is shorter: the iliac region is reached with a couple of tunnellings (the catheter needle can be bent during the insertion to follow the curves of the patient); local anaesthesia is quickly accomplished during the insertion of the catheter needle. The only disadvantage over the traditional technique is probably the cost.

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REFERENCE

Carl, P., Crawford M. E., and Ravlo, O. (1984). Fixation of extradural catheters by means of subcutaneous tissue tunnelling. *Br. J. Anaesth.*, **56**, 1369.

Sir,—We have found Dr Campailla's modification most interesting. Having dealt with this rather technical aspect of the treatment of chronic pain for several years, our experience is that any improvement of the tunnelling technique appears, in some way or other, to be advantageous to the patient.

There seem to be three major problems related to this topic: avoiding accidental withdrawal, reducing the likelihood of kinking of the catheter, and to minimize pain and other discomfort during the tunnelling procedure.

The number of nylon sutures attached to the catheter determines the degree of security against accidental withdrawal. However, this method necessitates several skin incisions. As indicated by Dr Campailla, an anterograde tunnelling technique is possible utilizing specially produced cannulae. Initially, in our Department, we used a 34-cm long flexible tunnelling cannula designed for this purpose. Because of high cost and metal fatigue, only allowing re-use four to six times, we abandoned this method and returned to the original retrograde procedure, using the 120-mm cannula. This procedure lasts approximately 15 min longer than the former, but allows more extensive suturing.

As illustrated above, alternative methods exist and with the co-operation of industry a standard extradural tunnelling kit may be presented in the near future! Nevertheless, until that day, we are all dependant of new information from colleagues in similar clinical situations.

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ANTAGONISM OF NEUROMUSCULAR BLOCKADE

Sir,—Several workers have shown that glycopyrrolate has advantages over atropine when used with neostigmine for reversal of neuromuscular blockade. It causes less tachycardia (Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977; Cozanitis et al., 1980; Bali and Mirakhur, 1980) and has a longer duration of action (Ramamurthy, Shaker and Winnie, 1972; Cozanitis et al., 1980). Most workers have studied combinations using neostigmine 2.5 mg. There are no reports following neurosurgical operations, where it is the normal practice in our hospital to use neostigmine 5 mg, when large doses of neuromuscular blockers have been used. We compared atropine 1.8 mg and glycopyrrolate 1 mg given with neostigmine 5 mg in the antagonism of neuromuscular blockade following various neurosurgical operations.

One hundred and ninety-one patients aged 16–78 yr (mean 53 yr) were studied. The anaesthetic technique was not standardized, but usually consisted of thiopentone, suxamethonium, tubocurarine and papaveretum with intermittent positive pressure ventilation using nitrous oxide, oxygen and halothane. Trimetaphan, sodium nitroprusside and beta-adrenoceptor antagonists were used in selected patients. Bradycardia was treated with atropine in 12 patients. The technique for the reversal of neuromuscular blockade and the re-establishment of spontaneous ventilation was standardized; patients were allocated at random to receive either mixture. Records of heart rate and arterial pressure were made immediately before reversal, then every 30 s for 5 min and every 1 min for 5 min more. Two-sample t tests, chi-squared tests for two-way tables, and log rank tests for survival data, were used as appropriate.

At reversal 102 patients received atropine and 89 patients glycopyrrolate. No significant differences existed between the two groups for age, sex, type of operation, premedication, anaesthetic technique or hypotensive technique. Of the patients given atropine during operation, three were included in the atropine reversal group and nine in the glycopyrrolate reversal group. This difference was statistically significant ($P < 0.05$). No significant differences existed between the pre-reversal values of heart rate and arterial pressure in the two groups. No significant difference existed between reversal groups for the arterial pressure increase following reversal. The mean increase in heart rate after reversal was significantly greater ($P < 0.001$) in the atropine group (70 ± 1 SEM beat min^{-1} increasing by 29 ± 2 SEM beat min^{-1}) than in the glycopyrrolate group (68 ± 2 SEM beat min^{-1} increasing by 20 ± 2 SEM beat min^{-1}). The level of significance was reduced ($P < 0.005$) when the data were re-analysed with the 12 patients given atropine during operation excluded. Glycopyrrolate had a significantly longer duration of action than atropine ($P < 0.001$). In 54% of the atropine, and 27% of the glycopyrrolate groups, heart rate had decreased below the pre-reversal value by 4 min; after 10 min the equivalent figures were 82% and 60%.

These results are consistent with those from other groups of patients (Mirakhur and Dundee, 1983). Ramamurthy, Shaker and Winnie (1972), Ostheimer (1977) and Mirakhur, Jones and Dundee (1981) showed that glycopyrrolate is roughly twice as potent as atropine. Our results demonstrate that this potency ratio is maintained at the higher doses needed in combination with neostigmine 5 mg. Tachycardia has not, itself, been shown to increase morbidity following neurosurgery, but can increase arterial pressure in some patients. Rapid increases in arterial pressure after neurosurgery can cause haematoma formation (Greenbaum, 1976). Therefore, at least theoretically, it seems desirable to avoid tachycardia following neurosurgery. The poor penetration of glycopyrrolate across the blood–brain barrier (Ramamurthy, Shaker and Winnie, 1972; Proakis and Harris, 1978) may also be advantageous: Baraka and colleagues (1980), Heinonen, Salmenparä and Takkunen (1982) and Cozanitis, Paloheimo and Jones (1983) demonstrated earlier post-anaesthetic arousal following glycopyrrolate–neostigmine, rather than atropine–neostigmine, mixtures.

We conclude that the administration of a glycopyrrolate–neostigmine, rather than atropine–neostigmine, mixture following neurosurgery may be beneficial. It seems logical to extend this recommendation to this reversal of neuromuscular blockade following neuroradiological procedures.

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SIDE EFFECTS INDUCED BY SUXAMETHONIUM ON THE SKELETAL MUSCLE AND THEIR PREVENTION

Sir,—Side effects induced by suxamethonium on the skeletal muscles (including increased serum concentrations of potassium, myoglobin, creatine kinase (CK) and myalgia) as well as their prophylaxis remain a subject of clinical and scientific interest.

The findings of Magee and Gallagher (1984) concerning serum potassium contrasted distinctly with our own. These authors found not only a sustained decrease below pre-induction values (up to 7 min following suxamethonium), but also a concentration lower than in the (untreated) control group. Our own studies (Plötz, 1984) showed not only a sustained increase above pre-induction values (up to 15 min following suxamethonium), but also a concentration at a higher level than in the control group.

The causes of these contradictory findings are not clear; however, differences existed in respect to age of the patients, and drugs used. Magee and Gallagher apparently studied adults anaesthetized with thiopentone whereas our observations concerned children under halothane–nitrous oxide–oxygen anaesthesia. Possibly the skeletal muscles react differently in respect to potassium release, depending not only on the type of anaesthetic (Dhanaraj et al., 1975) but also on the age of the subject. This certainly occurs in regard to incidence and extent, in adults, for myalgia (Bush and Roth, 1961) and in children, for hyper-CK-aemia (Tammisto, Leikkonen and Airaksinen, 1967) and hypermyoglobinaemia (Inagaki et al., 1980).

We have carried out further studies exclusively with children under halothane anaesthesia in which self-taming did not prevent the increases in serum CK activity. On the contrary, the activity was greater than in the control (Plötz and Braun, 1982). Dantrolene 2×1 mg kg^{-1} was ineffective in hindering or reducing the increase in serum potassium; here also even increases of the initial concentration of potassium were observed (Plötz, 1984), a noticeable occurrence (Agoston, 1979) in earlier studies also (Collier, 1979). Dantrolene has nevertheless proved itself effective in preventing hyper-CK-aemia (Plötz, Braun and Stallenberger, 1981) and hypermyoglobinaemia (Plötz, 1984).

Taking bibliographical references into consideration, Magee and Gallagher reach the conclusion (in spite of their findings) that self-taming has only limited clinical application. As shown by the cited papers, this method appears to bring no benefits whatsoever at least in regard to children. In any case, the multitude of proposed preventive measures as well as contradictory evidence in clinical studies indicate that the problem of side effects on the skeletal muscles induced by suxamethonium apparently cannot be solved by a single comprehensive method.

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Sir,—Thank you for this opportunity to reply to the comments made by Dr Plötz. When Baraka (1977) introduced the concept of "self-taming" he commented on the reduced incidence of suxamethonium-induced fasciculations, a phenomenon also observed by Plötz (1984). In this light it is interesting to note that the results of Dr Plötz are at variance with our own. However, serum potassium is affected by many anaesthetic agents, and there are differences in the agents used in the two studies.

When anaesthesia is induced with thiopentone followed by nitrous oxide–oxygen, there is a decrease in serum potassium concentration, possibly because of its entry into cells as a result of altered cellular metabolism (Bali, Dundee and Assaf, 1975). Where suxamethonium is administered the increase in plasma potassium concentration is less marked following thiopentone induction than following halothane (Henning and Bush, 1982), and halothane also alters the timing of the increase in serum potassium where a delay in peak effect is seen (Bali, Dundee and Assaf, 1975). We agree with Dr Plötz that there may also be differences in the reaction of children as compared with adults. We feel that these differences may explain Dr Plötz's results, and confirm our own conclusions that the technique has limited clinical applicability.

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NALOXONE—A STRONG ANALGESIC IN COMBINATION WITH HIGH-DOSE BUPRENORPHINE?

Sir,—Buprenorphine is a synthetic opiate, with partial agonist and antagonist properties. The dose–response curve as far as analgesia is concerned is bellshaped when determined in animals (Rance, Lord and Robinson, 1979; Dum and Herz, 1981). This curve has not been determined in man. Naloxone is an opiate antagonist without intrinsic agonist activity.

It has been shown by Rance, Lord and Robinson (1979), in animal studies, that prior treatment with naloxone significantly reduced the analgesic action of low doses of buprenorphine. On the other hand, with the use of high doses of buprenorphine (above the maximum of the biphasic dose–response curve) prior treatment with naloxone potentiates the agonistic properties of buprenorphine; for example, the dose–response curve is shifted to the right. Dum and Herz (1981) injected naltrexone and found a symmetrical shift of the entire buprenorphine dose–response curve to the right. As a result, the agonist potency of the higher doses of buprenorphine was actually increased by the antagonist (naltrexone).

We have used buprenorphine in doses of 30 and 40 μg kg^{-1} as the sole i.v. analgesic in balanced anaesthesia to patients scheduled for cholecystectomy.

Two otherwise healthy females patients (19 and 28 yr) were premedicated with diazepam 0.3 mg kg^{-1} orally 2 h before surgery. One patient received buprenorphine 40 μg kg^{-1} the other 30 μg kg^{-1}. After 15 min anaesthesia was induced with diazepam 0.1 mg kg^{-1} and thiopentone 2–3 mg kg^{-1}. The patients received pancuronium 1 mg as precurarization, and oral intubation was facilitated with suxamethonium 1.5 mg kg^{-1}. Droperidol 2.5 mg was used as an antiemetic. The lungs were ventilated using a mixture of 70% nitrous oxide in oxygen. Muscle relaxation was maintained with pancuronium. No objective signs of pain were observed during surgery. The durations of surgery were 75 and 105 min. Neuromuscular blockade was antagonized using a mixture of neostigmine 2.5 mg and atropine 1 mg.

Immediately following the termination of anaesthesia both patients complained of severe pain, which was aggravated by deep inspiration. In an attempt to counteract what was assumed to be an antagonistic effect of buprenorphine, naloxone was administered i.v. in repeated small doses to a total of 0.08 and 0.4 mg, respectively, and was followed by total pain relief. The patients could breathe deeply without pain and were only slightly sedated. Respiration was adequate, as judged by respiratory rate and arterial blood-gas analyses. Following the injection of naloxone, the patients were without pain for 17 and 21 h, respectively. They then received buprenorphine 0.3 mg i.m. with good effect.

A possible explanation for these events could be that the high doses of buprenorphine resulted in antagonistic dominance, leading to insufficient pain relief. We counteracted this unintended effect, using a pure opiate antagonist, naloxone, which induced adequate pain relief of long duration. These observations are in agreement with the results found in the earlier studies on animals.

Two immediate questions come to mind: how can such a small dose (0.08 mg) of a short-acting drug such as naloxone have such a prolonged effect (17 h)?, and how is it that a dose of buprenophine that was unable to obtund the severe pain immediately after the operation was effective as sole analgesic element of anaesthesia during the cholecystectomy? Further speculation based on our limited data would be fruitless, and controlled studies in man are needed to elucidate these matters.

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RESPIRATORY PROBLEMS AFTER ATROPINE AND NEOSTIGMINE IN DOGS

Sir,—Jones and Clutton (1984) reported that, in their series of 22 canine patients given atracurium besylate, one dog which showed normal reversal of neuromuscular blockade following the injection of atropine and neostigmine, and which was observed 5 min later to have good respiratory function, developed cyanosis with obviously inadequate respiratory movements over the next 5-min period. The problem was resolved by re-intubation, respiratory support with oxygen and the injection of a further dose of neostigmine with atropine.

We have recently experienced what appeared to be a similar problem in two of 66 dogs which were observed to have good respiratory function for several minutes after reversal of atracurium-induced neuromuscular blockade with neostigimine and atropine. One dog stopped breathing 15 min later and the other 25 min later. During these periods both dogs were under constant nurse surveillance and resuscitative measures were instituted promptly.

The incidence of 1 in 22 cases as reported by Jones and Clutton and 2 in 66 of our cases is a cause of some concern to veterinary anaesthetists and we would be interested to learn whether any similar problems have been encountered in the use of atracurium in man.

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REFERENCE

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BOOK REVIEWS

Manual of Pediatric Anesthesia (2nd Edn). By David J. Steward. Published by Churchill Livingstone. Pp. 377; indexed. Price £24.00.

A prolific author and editor, David Steward was, for more than 10 years, Anaesthetist-in-Chief to the Hospital for Sick Children (HSC) Toronto ("the largest children's hospital in North America") where 14000 operations are performed annually.

His *Manual of Pediatric Anesthesia* first appeared in 1979. The second edition, to which all members of HSC anaesthetic staff have contributed, brings the first up-to-date and extends it by some 50 pages. It remains a taut, relatively inexpensive volume in a clear uniform format, with the same provision as its forerunner: (1) anatomy and physiology considerations, (2) principles of paediatric anaesthesia management, and (3) descriptions of techniques used at HSC.

The first two provisions are concisely and clearly achieved. Several other recent texts have, however, covered these fields. What makes this volume outstanding is the authoritative and straightforward outline advice given regarding a very wide range of clinical circumstances. Many of the areas covered will be of direct interest only to anaesthetists in sub-specialty practice, but everyday problems (for example strabismus, circumcision, hernia) are accorded equally thorough attention, and all who regularly anaesthetize children will wish to own a copy.

The book is full of tips and checklists, useful for clinical practice and for teaching. Few will agree with every uncompromising instruction, but the unashamed dogmatism will certainly provoke the reader to think.

Present Canadian practice evidently contrasts with British practice in some particulars. The book scarcely mentions enflurane (do not use it in phenylketonuric patients), but isoflurane is recommended in a wide range of situations. Methoxyflurane is often recommended, but atracurium and vecuronium receive no mention. S.I. units are not used, even in parentheses.

There are also some errors—mostly self-explanatory, some confusing (calcium gluconate 10% solution is recommended in dosages of 2 μl, 10 mg/kg and 10 mEq/kg on different pages).

Nevertheless, the book might be worth its cost for the table of rarer disorders alone, backed with the 118 references to these and their anaesthetic management. Dull reading, but invaluable when that rare syndrome presents for surgery.

The book is highly recommended, even to those who already possess a first edition.

William R. Hain

Year Book of Anaesthesia (1984). Edited by Ronald D. Miller. Published by Blackwell Scientific Publications, Oxford. Pp. 391; indexed; illustrated. Price £38.00.

This is the latest edition of a well established series. There is now such a vast range of information published that it is virtually impossible for practising anaesthetists to be familiar with more than a fraction of original work. This volume attempts to present a representative selection of recent literature from 69 different journals. The editor, R. D. Miller, was assisted in the task by R. R. Kirby, G. W. Ostheimer, L. J. Saidman and R. K. Stoelting. There are 13 chapters, covering most aspects of anaesthetic practice. Three of these, The Informed Anaesthetist, Anaesthetic Risks and Epidural Narcotics are small (6, 4 and 4 pages, respectively) and could have been incorporated in the other chapters.

The selected articles are presented in abstract form and each is followed by comments from one of the editorial staff. These are an excellent feature: some put the article in context with other work in the same field, some indicate which papers deserve to be read in full, mention a special merit or occasionally point out flaws. Thus the reader gains an appreciation of the content not possible with abstracts in isolation. The main theme of the comments was the clinical implication of the work published; even the more scientific papers were judged on this basis. Some comments, notably those of Ostheimer, amounted to mini-reviews of the subject. A good example was his clear chronological review of the use of extradural narcotics. There was a reasonable balance between the scientific and clinical in the articles presented but, not surprisingly, they reflected mainly North American practice.

It is not appropriate to mention specific articles of personal interest. The value of the Year Book is to enable the reader to remain aware of the ever-expanding volume of knowledge across the broad front of anaesthetic practice. The price of £38.00 may appear expensive, but it is less than the average subscription to a single journal. It merits inclusion in all departmental libraries.

James E. Caldwell

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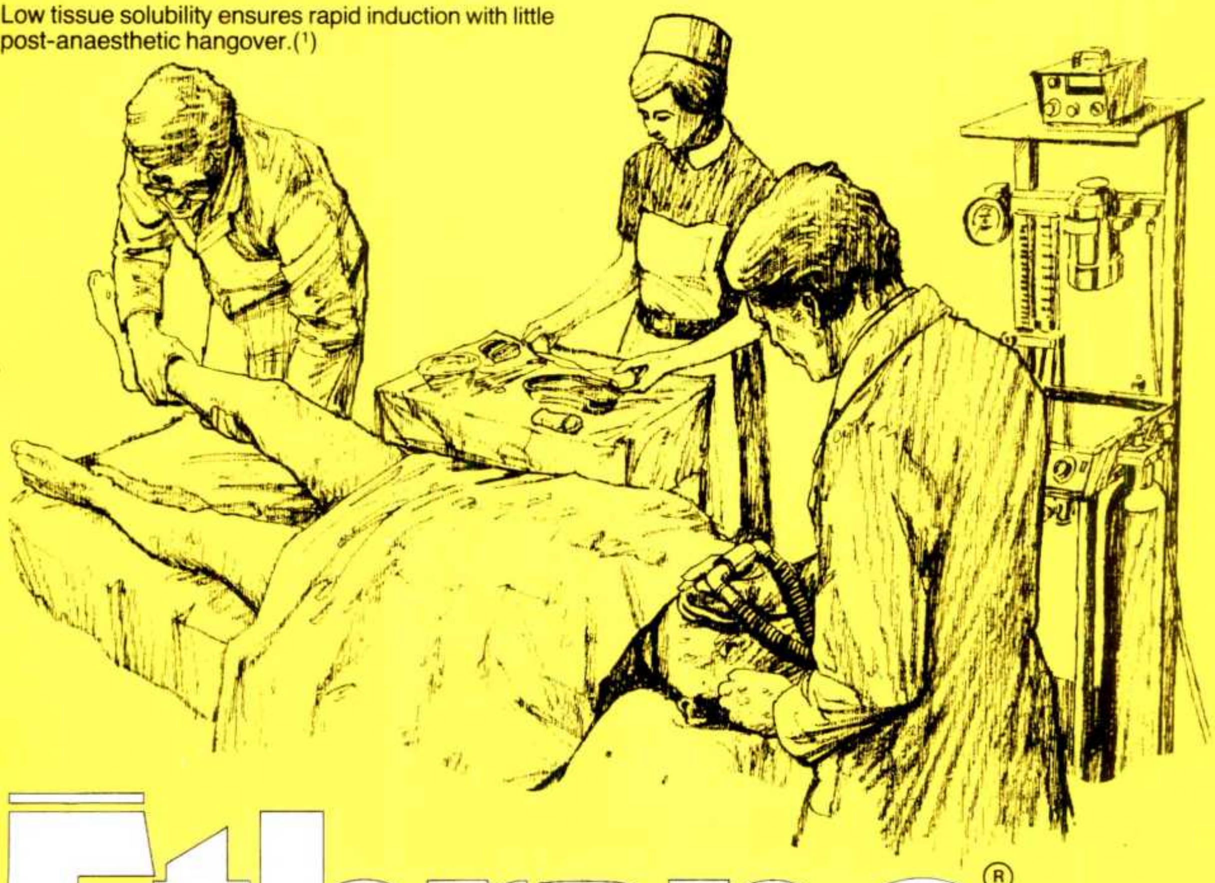

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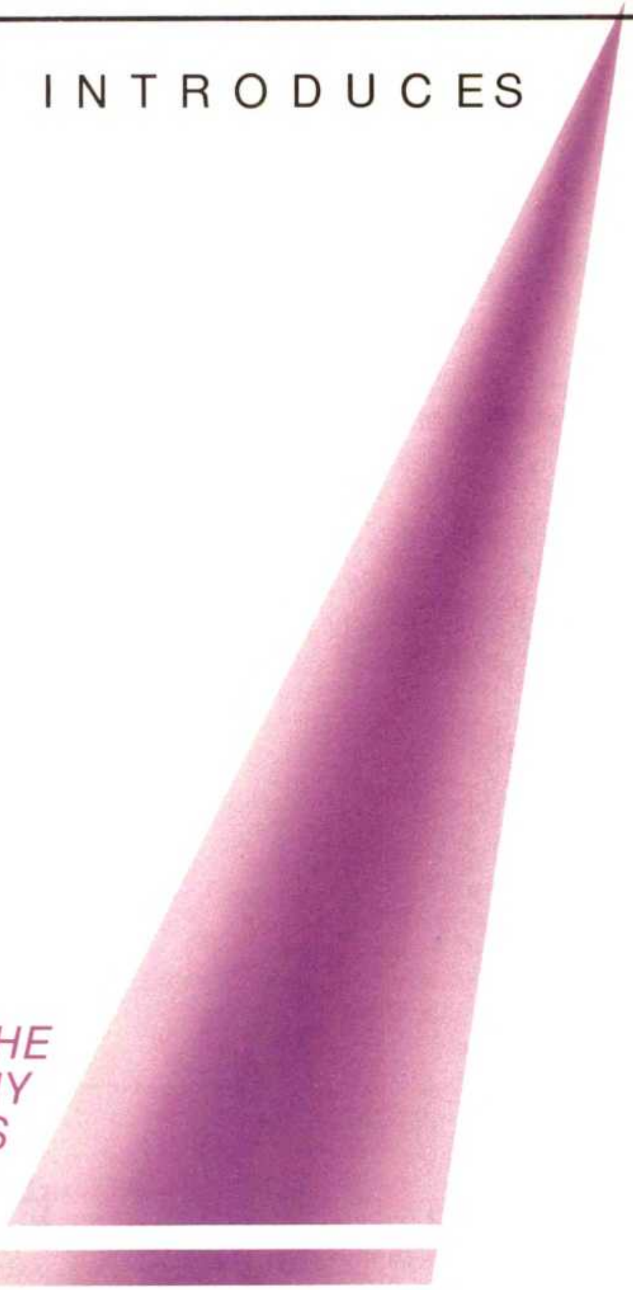

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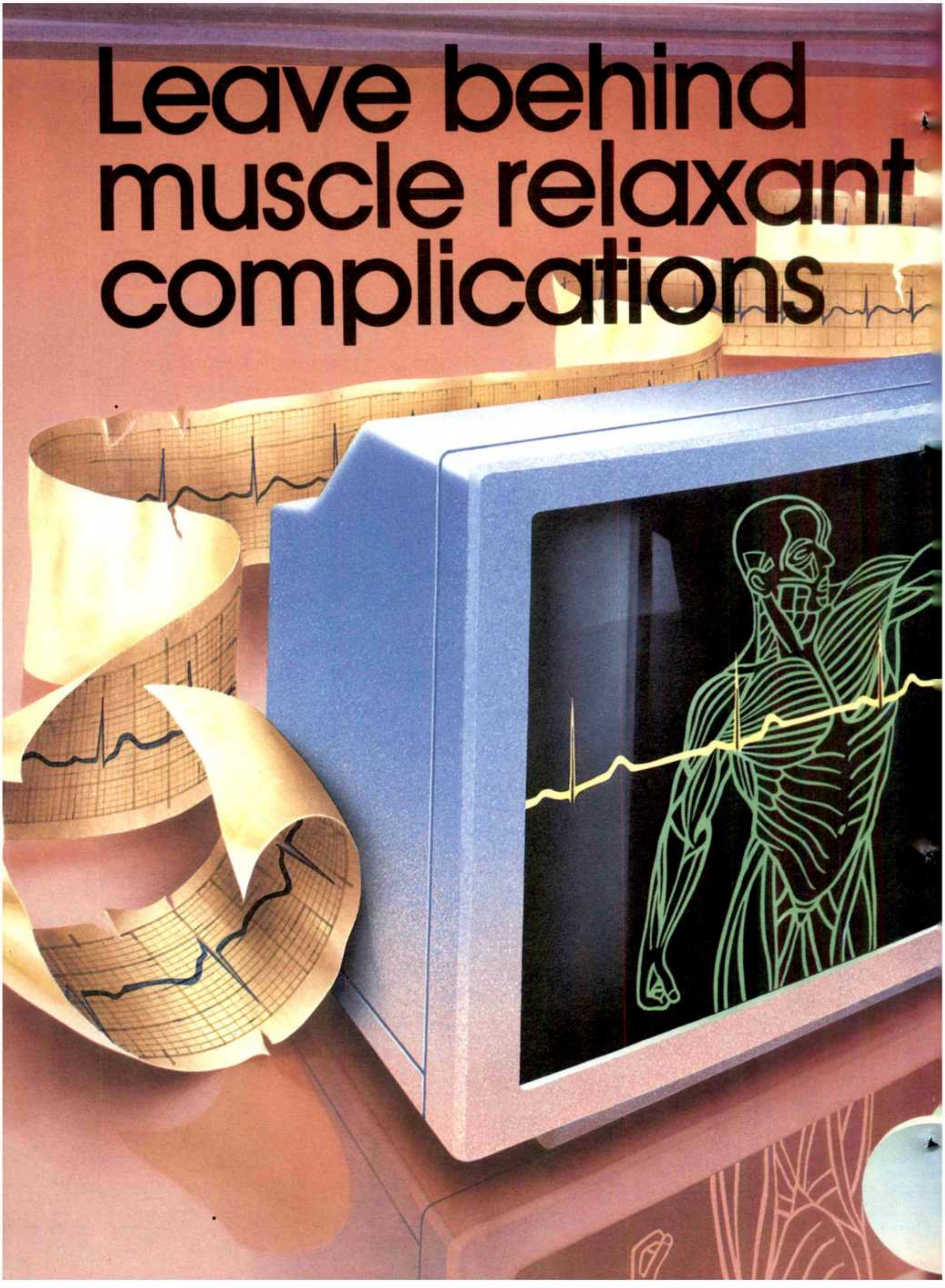

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1. Feldman SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 199-200
2. Basta SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 183-184

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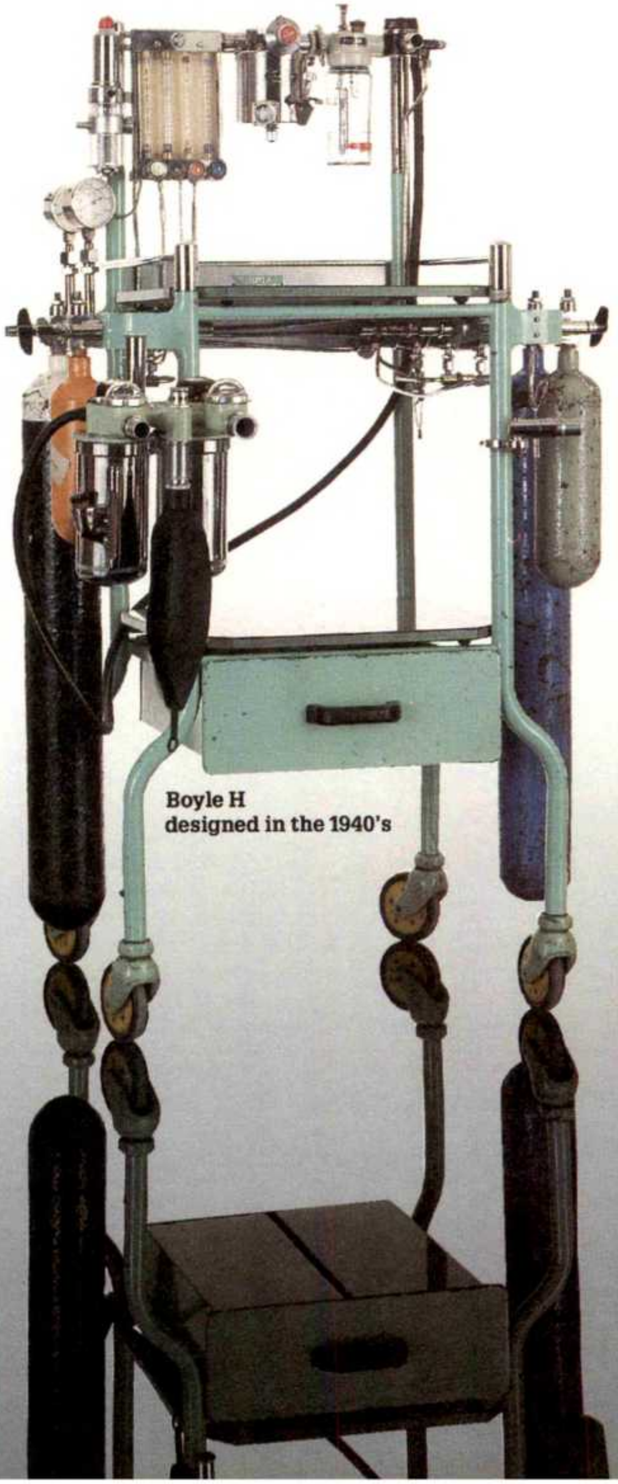

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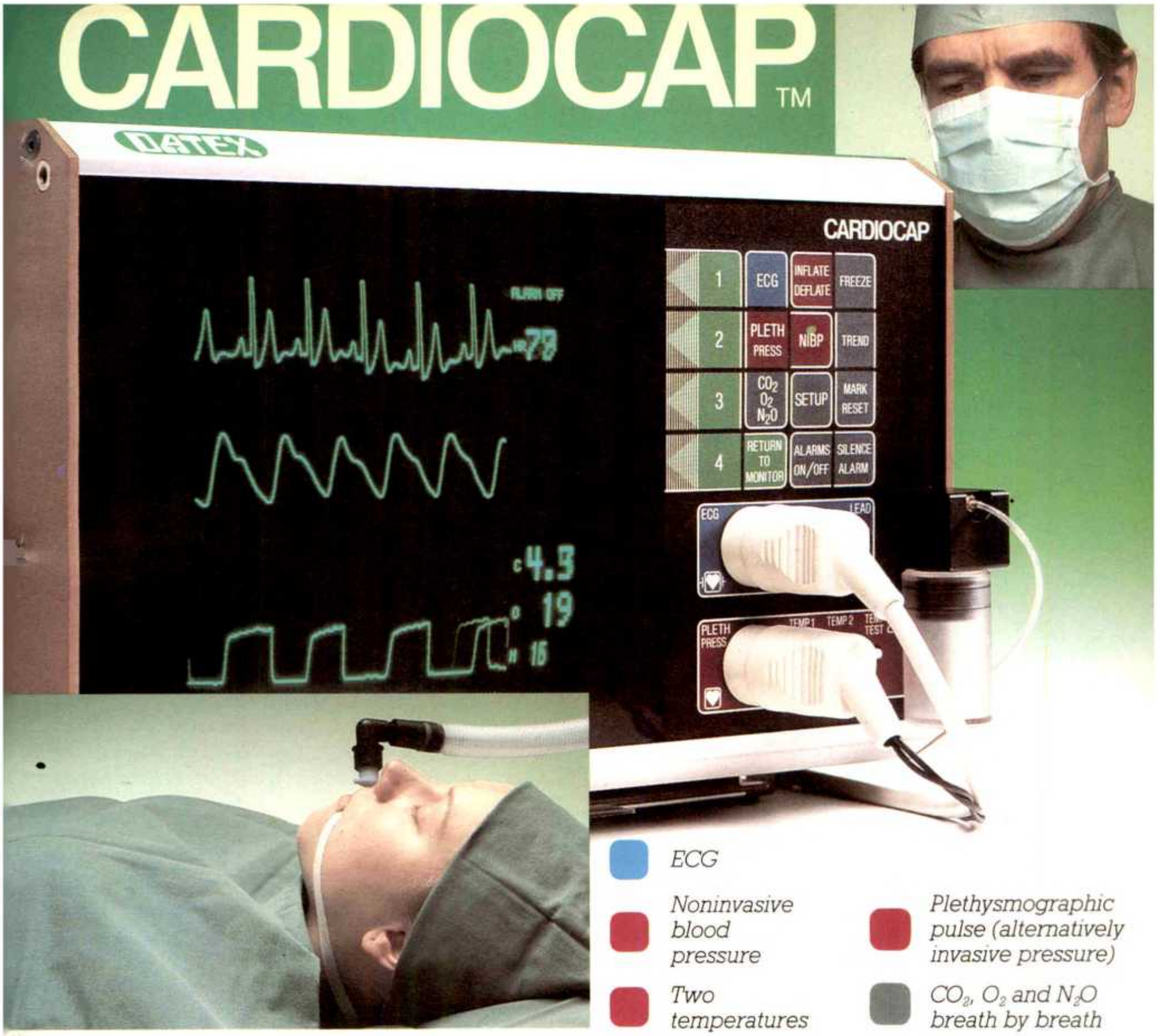

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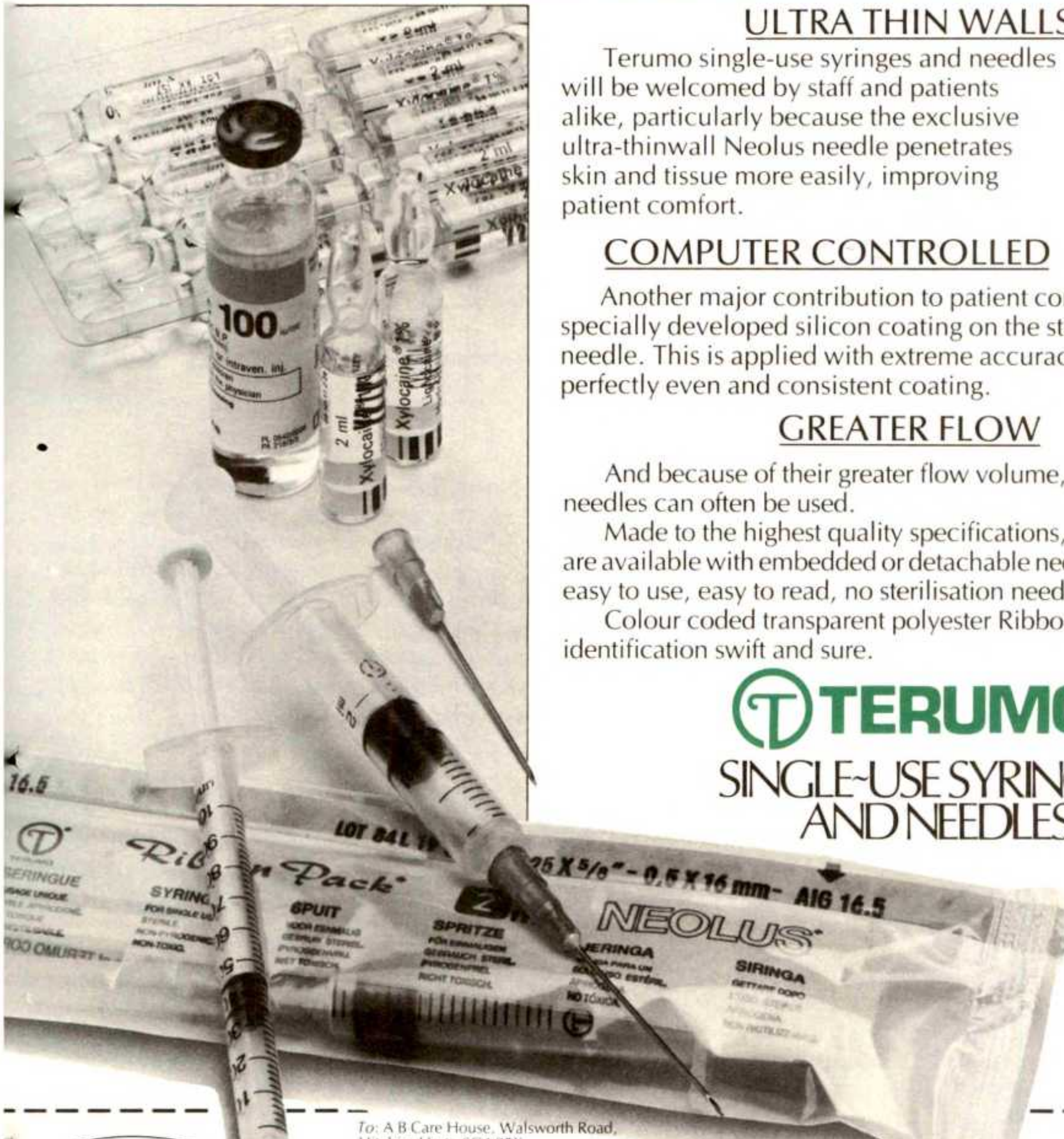

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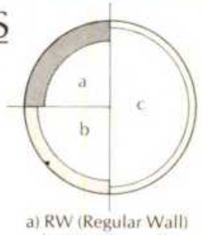

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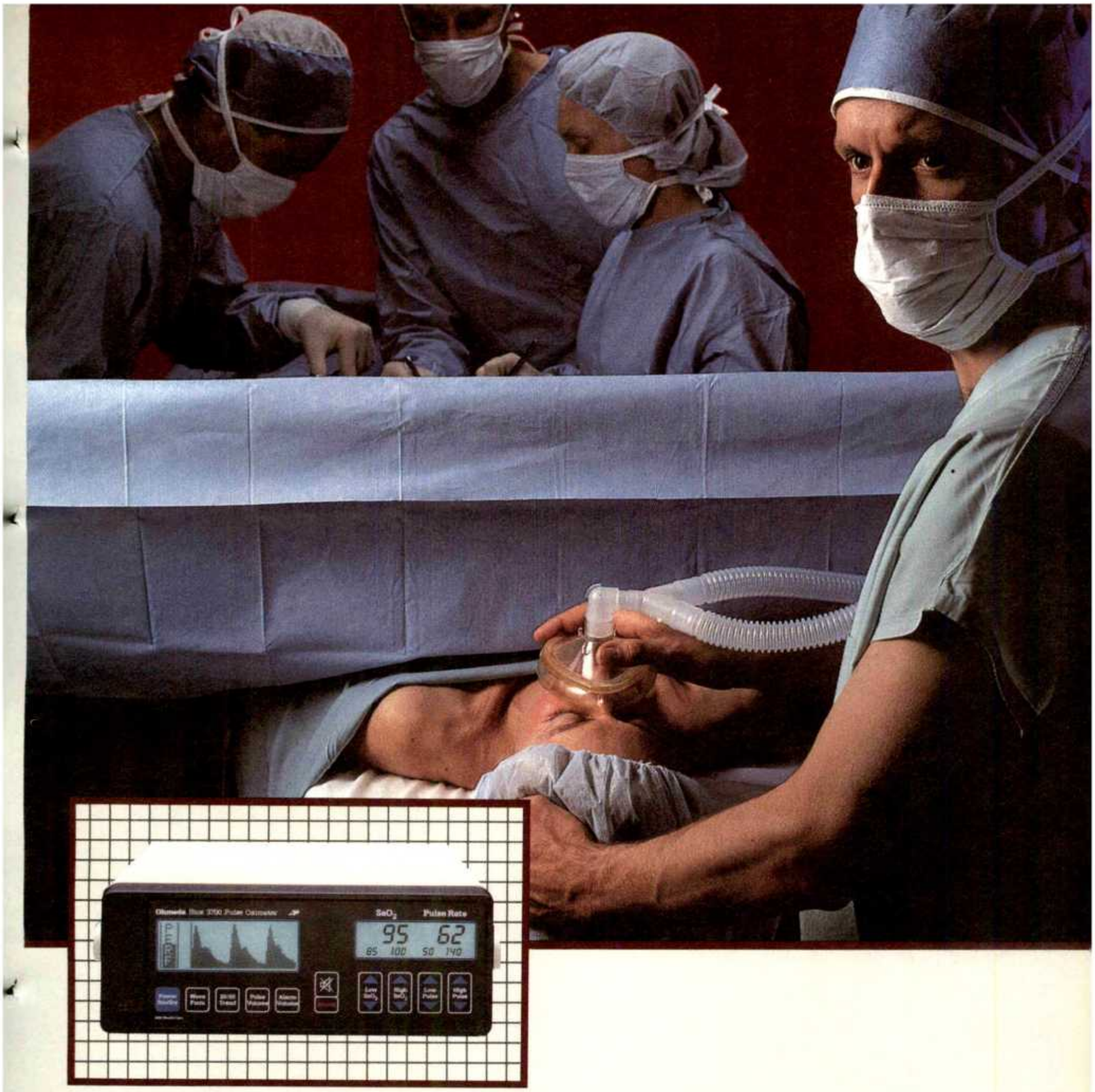

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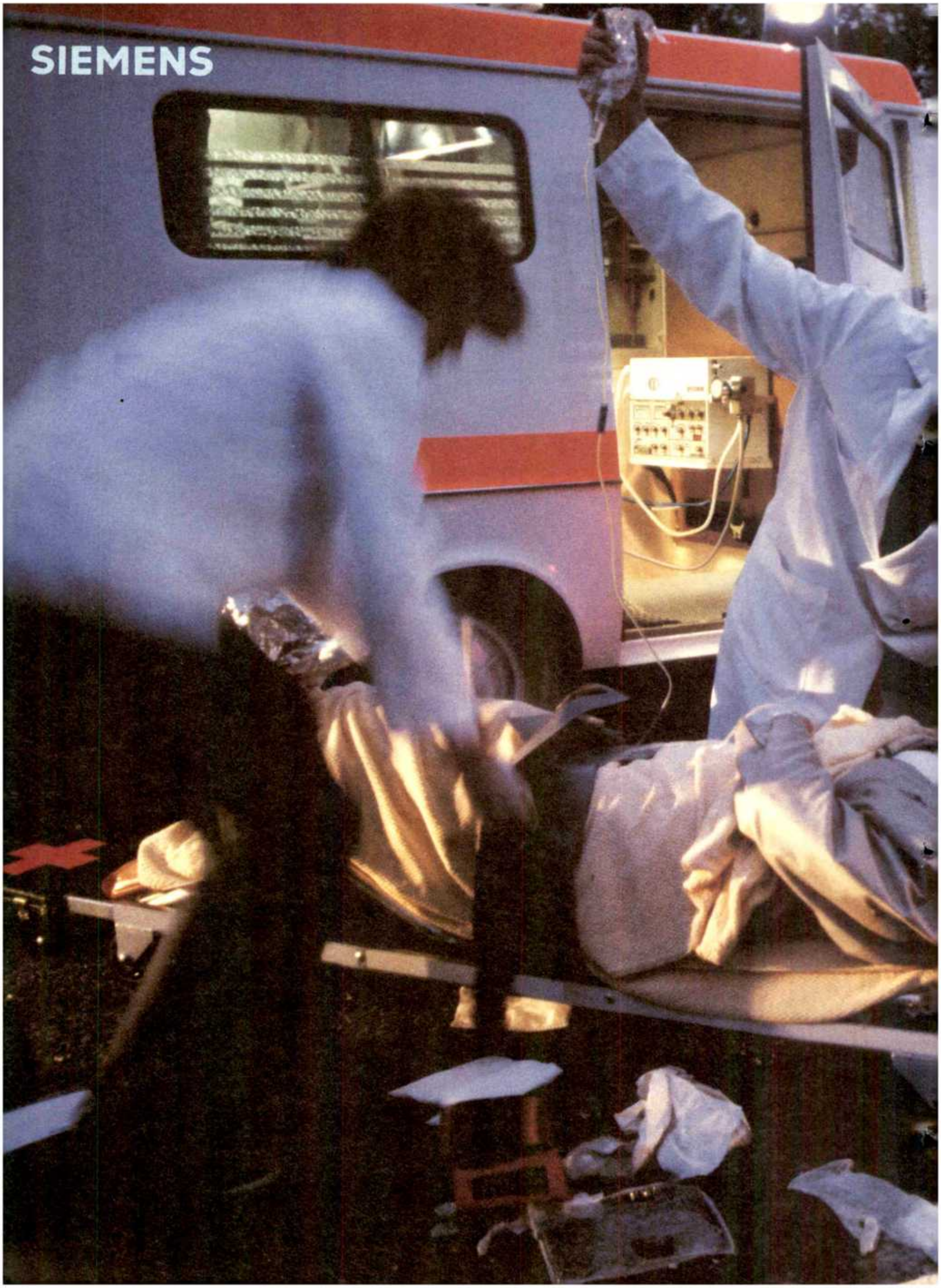
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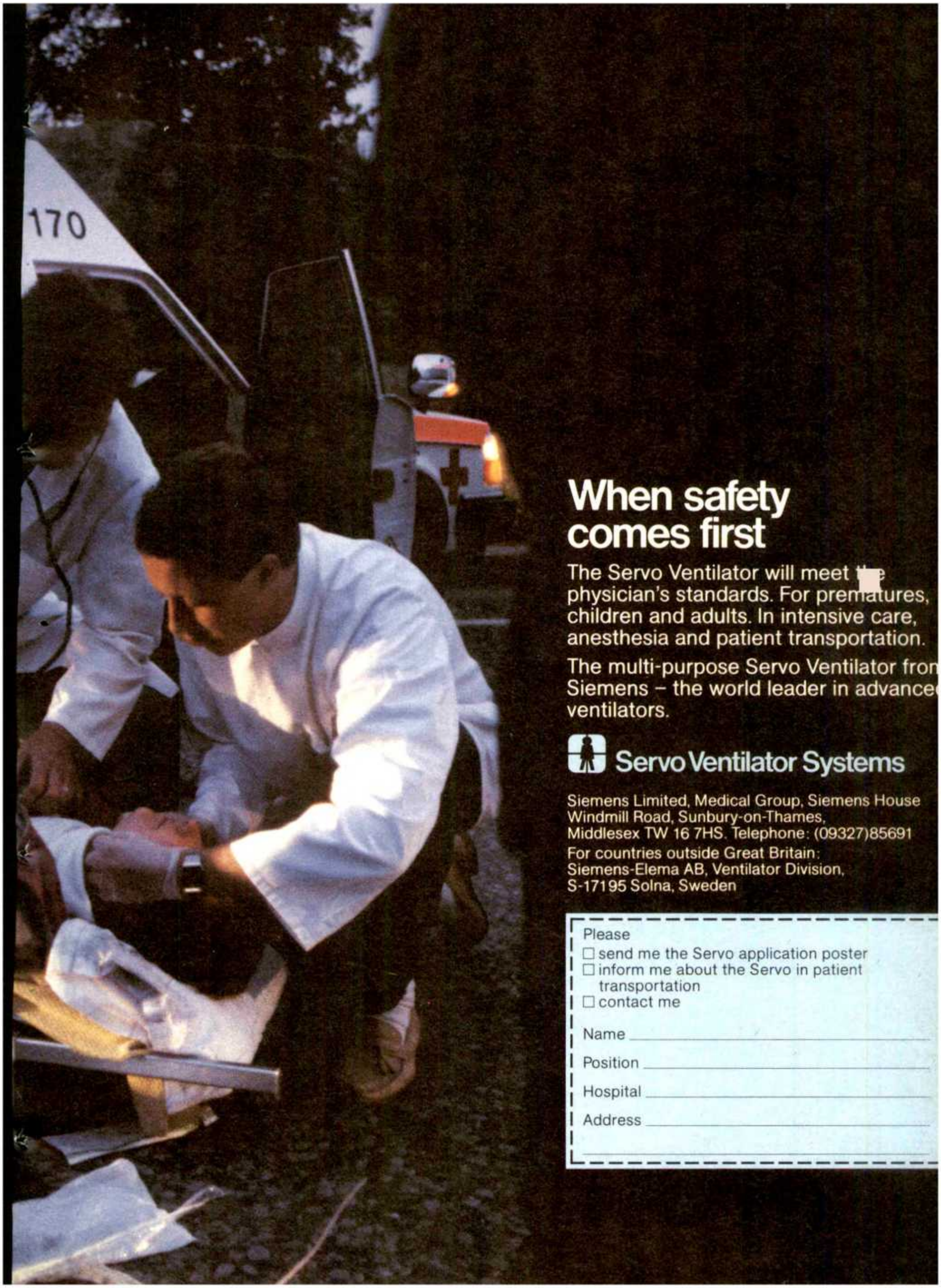

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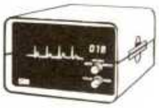

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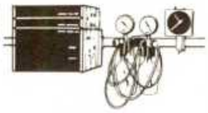

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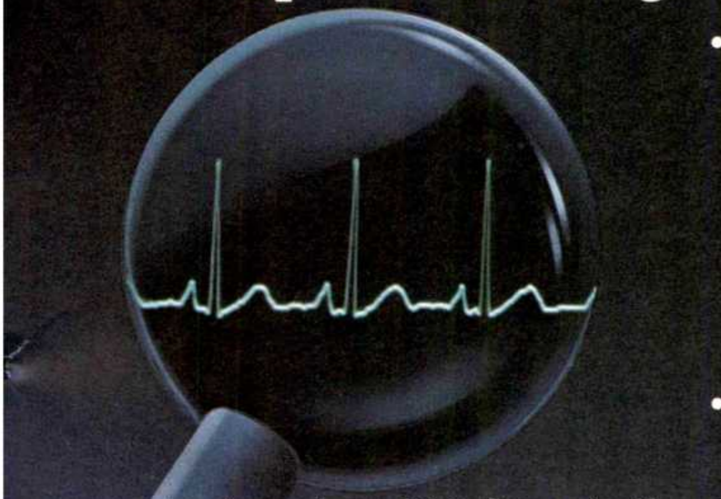

- **AErrane™ (isoflurane) causes a dose-related decrease in peripheral resistance (and cardiac afterload) but little or no depression of myocardial function or cardiac output** (at normal levels of surgical anaesthesia, 1 to 1.5 MAC).[2] These effects are potentially useful in the elderly;[3] in patients with coronary artery disease,[4] and for induced hypotension in cerebral aneurysm surgery.[5]
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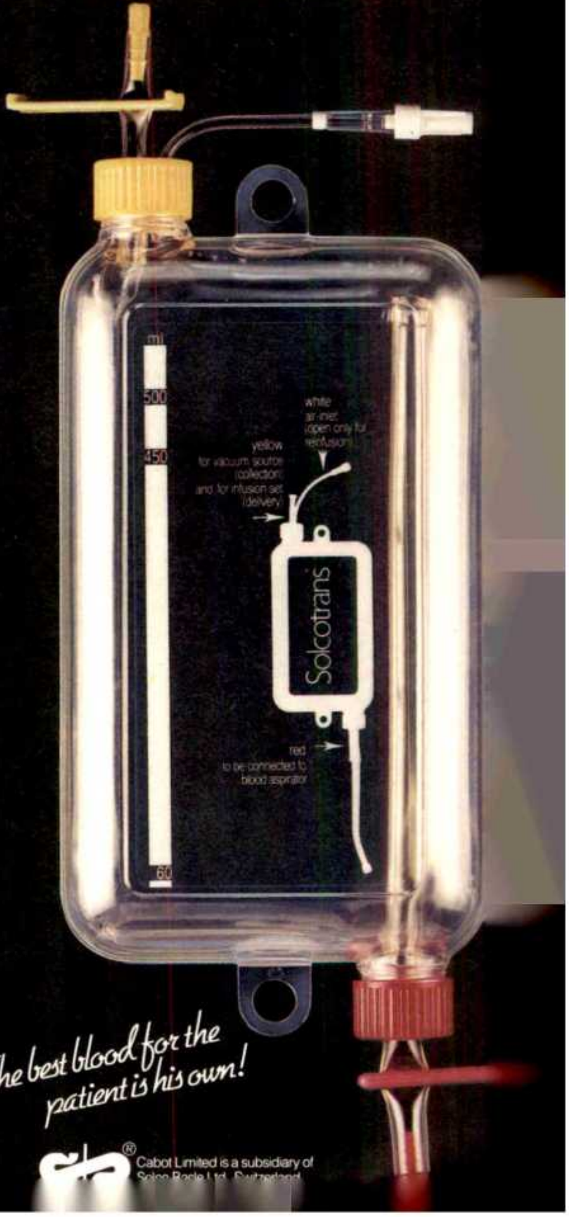
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EFFECT OF RENAL FAILURE ON LAUDANOSINE EXCRETION IN MAN

M. R. FAHEY, S. M. RUPP, C. CANFELL, D. M. FISHER, R. D. MILLER, M. SHARMA, K. CASTAGNOLI AND P. J. HENNIS

SUMMARY

Patients with renal failure and undergoing a cadaver renal transplant were found to have plasma concentrations of laudanosine, following the administration of a single bolus dose of atracurium 0.5 mg kg^{-1}, higher than those found in patients without renal failure. Since laudanosine is a known central nervous system stimulant in a variety of animal species, its actions should be investigated further in man, and particularly in patients with renal failure.

Although atracurium, *per se*, does not produce prolonged neuromuscular blockade in patients with renal failure (Hunter, Jones and Utting, 1982; Fahey et al., 1984), the influence of renal failure on the elimination of its metabolites has not been determined in man. Of the major metabolites of atracurium, laudanosine is of particular interest since it has central nervous system (CNS) stimulant properties in animals (Babel, 1899; Mercier and Mercier, 1955). We have determined the influence of renal failure on the excretion of laudanosine in patients receiving atracurium to provide muscle relaxation during surgical procedures.

PATIENTS AND METHODS

Sixteen patients were studied, after giving informed consent as approved by our Human Research Committee. Eight patients had normal renal function and were scheduled for elective surgery; the laudanosine concentrations in these patients were reported in an earlier publication (Fahey et al., 1984). The remaining eight patients had renal failure sufficient to necessitate haemodialysis. They were scheduled for cadaver kidney transplant and were dialysed within 24 h of surgery. All patients received diazepam 10 mg by mouth before surgery. Ninety minutes later, anaesthesia was induced with thiopentone 1–2 mg kg^{-1} i.v. and the inhalation of nitrous oxide and halothane in oxygen via a face mask. The trachea was intubated without the use of neuromuscular blocking drugs, and ventilation controlled to maintain pH between 7.35 and 7.40. Anaesthesia was maintained with 0.6% end-tidal halothane and 60% nitrous oxide in oxygen, as measured continuously by mass spectrometry. Pharyngeal temperature was maintained at 37 °C with surface warming.

Once stable anaesthetic conditions had been achieved (approximately 30 min after endotracheal intubation) atracurium 0.5 mg kg^{-1} was injected as in i.v. bolus. Venous blood samples were obtained from a separate i.v. cannula at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min after the injection of atracurium. These samples were heparinized, immediately acidified with sulphuric acid 3 mol $litre^{-1}$ so that the plasma achieved a pH of 5.0 ± 0.5, centrifuged in the operating room, and the plasma frozen to −20 °C until analysis. No additional doses of atracurium were given to maintain surgical relaxation; instead, suxamethonium was administered by infusion, as required.

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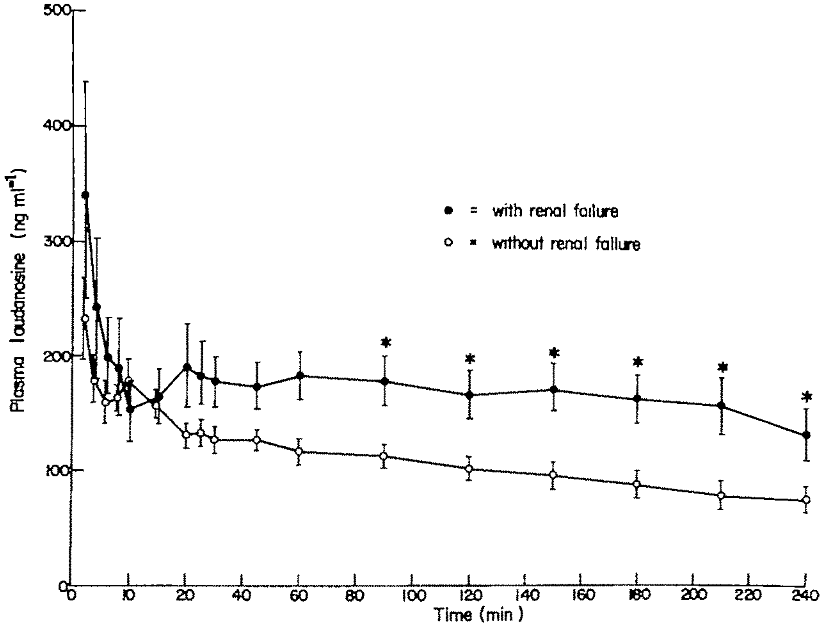

FIG. 1. Mean plasma laudanosine concentrations (±SEM) *v.* time. *Sampling times with a statistical difference between patient groups.

Concentrations of laudanosine were determined using gradient ion-exchange liquid chromatography with a sodium sulphate 0.06 mol litre^{-1} (pH 2.0) and acetonitrile mobile phase and N-methyl-laudanosine as an internal standard (Fahey et al., 1984). The assay was sensitive to a laudanosine concentration of 10 ng ml^{-1} with a coefficient of variation of 9 % at 15 ng ml^{-1}. Mean values for laudanosine concentrations for the two patient groups at each time interval were compared using the Mann–Whitney test (Zar, 1974). $P < 0.05$ was considered significant.

RESULTS

Mean plasma laudanosine concentrations were greater in the patients with renal failure between 90 min and 240 min after the injection of atracurium than those found in the patients without renal failure (fig. 1). There were no differences in mean plasma laudanosine concentrations before the 90-min sampling time. The highest laudanosine concentration in the patient group without renal failure was 327 ng ml^{-1}; that in the renal failure group was 758 ng ml^{-1}. These peak values were observed in the first 10 min following the administration of the atracurium. The time from the administration of atracurium until perfusion of the transplanted kidney was between 50 and 120 min; renal function *per se* was not assessed until the day following surgery.

DISCUSSION

Patients with renal failure may have prolonged neuromuscular blockade from non-depolarizing neuromuscular blocking drugs because of the dependence of these drugs on the kidney for their elimination. However, neuromuscular blockade associated with atracurium is not prolonged in patients with renal failure, because its metabolic breakdown is independent of renal function (Fahey et al., 1984). However, unlike the parent drug, the metabolites of atracurium may not be rapidly eliminated, and may possess potentially harmful effects such as the CNS stimulation associated with laudanosine (Babel, 1899) and the tissue alkylation resulting from the acrylate metabolites (Nigrovic and Koechel, 1984). These toxic effects could be accentuated if renal or liver disease increased the blood concentrations of these metabolites.

Laudanosine has been a subject of scientific investigation for 85 yr (Babel, 1899; Mercier and

Mercier, 1955), the major finding of which is that laudanosine is a CNS stimulant in a variety of animal species. Its effects may include seizures or an increase in anaesthetic requirement, both of which could conceivably go unrecognized in the patient receiving atracurium.

Animal studies have shown that the i.v. dose of laudanosine necessary to produce seizure activity is species-dependent. Rabbits can exhibit seizure activity with an i.v. dose of 3 mg kg^{-1} of laudanosine (Shi et al., 1985), whereas dogs require four to six times that dose to display a similar response (Mercier and Mercier, 1955; Hennis et al., 1984). Plasma concentrations of laudanosine which induce seizures in these animals have not yet been determined. Thus, at the present time, it is not possible to determine whether the concentrations of laudanosine present in patients with renal failure, after a single i.v. dose of atracurium, could affect the CNS.

No patient in this study exhibited gross evidence of CNS stimulation that could be attributed to laudanosine. However, Duncan (1983) reported a paediatric patient in renal failure who received atracurium 0.6 mg kg^{-1} and, after attempted antagonism of neuromuscular blockade with neostigmine 20 min later, exhibited unexplained "jerky movements of his limbs" and sweating—a clinical picture that could be explained in part by the pharmacological action of laudanosine. However, since neuromuscular blockade may mask any CNS effects, studies using electroencephalographic monitoring may be needed to provide a definitive answer.

Our results show that renal failure leads to significantly higher concentrations of laudanosine following the administration of a single dose of atracurium. Although not considered in this study, it is possible that repeated doses of atracurium could lead to higher concentrations of laudanosine than those reported, and be more likely to cause CNS effects.

In conclusion, we have demonstrated increases in the concentration of laudanosine following the administration of atracurium to patients with renal failure. This suggests that the kidney is involved in the elimination of laudanosine. Since laudanosine is considered a potent CNS stimulant in animals, studies should be undertaken in man in case its potential CNS effects are masked by neuromuscular blockade and general anaesthesia.

ACKNOWLEDGEMENT

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NEUROMUSCULAR BLOCKING EFFECTS OF ATRACURIUM, VECURONIUM AND PANCURONIUM DURING BOLUS AND INFUSION ADMINISTRATION

L. GRAMSTAD AND P. LILLEAASEN

SUMMARY

The potencies of atracurium, vecuronium and pancuronium were compared using bolus injections and continuous infusions. The sizes of the bolus injections were based on previously determined cumulative dose–response relationships. Dose requirements for 90% and 50% sustained blockade were estimated by use of continuous infusion, and the corresponding plasma concentrations were measured for vecuronium and pancuronium. The effect of single bolus injections correlated well with the cumulative dose–responses, confirming relative potencies for atracurium, vecuronium and pancuronium of approximately 1:5:4. The maintenance doses ($\mu g\ kg^{-1}\ h^{-1}$) for 90% blockade were: atracurium 382.8, vecuronium 101.9, and pancuronium 36.9, making the relative dose requirements 10.4:2.8:1. The same dose ratio was found for atracurium and vecuronium at 50% blockade. This required about 60% of the doses needed for maintenance of 90% response. The relative potency of vecuronium and pancuronium in plasma was 1.1:1. The 25–75% recovery index was significantly shorter for vecuronium than for atracurium.

Atracurium and vecuronium are recently introduced non-depolarizing neuromuscular blocking drugs with intermediate durations of action. Cumulation seems to be negligible, and recovery is relatively rapid with both drugs (Agoston et al., 1980; Payne and Hughes, 1981). Since comparative clinical evaluations of these drugs require a knowledge of the relative dose requirements associated with different techniques of administration, we estimated previously the dose–response relationship during initial neuromuscular blockade with these drugs using a cumulative dose regimen (Gramstad and Lilleaasen, 1982). In the present investigation we have evaluated these dose–effect relationships following a single bolus. In addition, the dose requirements for sustained neuromuscular blockade were estimated by the administration of continuous i.v. infusions of the drugs and the corresponding plasma concentrations were determined for vecuronium and pancuronium.

PATIENTS AND METHODS

Thirty patients (ASA class I) undergoing surgery on the ear, nose or parotid gland, with an expected duration of anaesthesia of more than 2.5 h, were investigated. Informed consent was obtained before the patients were randomly allocated to receive atracurium, vecuronium or pancuronium. Stratified sampling was used to obtain an even sex distribution. Exclusion criteria were: pregnancy, medication for infectious or other diseases, more than 20% deviation from normal weight, age less than 18 or greater than 60 yr.

Patients were premedicated with pethidine 50–100 mg and atropine 0.6 mg i.m. about 1 h before the induction of anaesthesia. After arrival in the operating theatre, sedation and analgesia were achieved with diazepam 5–10 mg and fentanyl 0.1–0.2 mg i.v. Subcutaneous needle electrodes were placed at the wrist, and supramaximal stimuli at 0.1 Hz were delivered from a nerve stimulator (Myotest). The evoked adduction force of the thumb was measured with a Statham UC3 transducer (with UL4-20 load cell) connected to a Hewlett–Packard 7702B recorder equipped with 8805C amplifier. Resting thumb tension was maintained between 200 and 300 mg throughout the study. When the evoked twitch

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response was stable, anaesthesia was induced with diazepam 5–10 mg, fentanyl 0.1 mg, and thiopentone 100–300 mg until the eyelash reflex disappeared.

ED_{95} doses of the neuromuscular blocking drugs (which had been estimated previously by the cumulative technique (Gramstad and Lilleaasen, 1982)), were given as a single bolus injection. The doses were: atracurium 279 μg kg^{-1}, vecuronium 56 μg kg^{-1} and pancuronium 64 μg kg^{-1}. Once the maximum effect had been obtained, the trachea was intubated, and ventilation was controlled using a Servo 900B ventilator equipped with a Siemens-Elema CO_2 Analyzer 930. Anaesthesia was maintained with 65 % nitrous oxide in oxygen, and increments of fentanyl were given as required. Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4 and 5 vol%. Rectal temperature was monitored with a Digimed H10 thermometer and was maintained between 35.0 and 37.0 °C in all patients.

Once the maximal effect of the initial dose had been achieved, the neuromuscular blocker was administered by a continuous infusion (Hoechst PP50 infusion pump). The drug solutions were prepared with physiological saline at 4 °C immediately before the induction of anaesthesia. The concentrations of the solutions were chosen such that the 50-ml infusion syringe should not normally have to be replaced during the investigation. The concentrations were: atracurium 1.8 mg ml^{-1}, vecuronium 0.4 mg ml^{-1} and pancuronium 0.16 mg ml^{-1}.

At first the rate of infusion was titrated to produce a constant 90 % twitch depression. After 60 min the rate of the infusion was held constant and the drug requirement and the twitch response were noted. After a subsequent 15-min period of constant-rate infusion, the twitch response was re-assessed, and the individual change in response during the 15-min time interval recorded. The infusion pump was then stopped and was restarted about 4 min before the twitch height was expected to reach 50%. The rate of infusion was then titrated to produce a constant 50 % depression of the control twitch force. After 30 min the infusion rate was held constant; the drug requirement was noted and the twitch response was measured at the start and end of a subsequent 15-min period, as undertaken previously.

An additional dose of neuromuscular blocker equal to one-third of the initial bolus dose, was then given as a single injection. After the maximal effect had been achieved, the infusion was discontinued, and the recovery time from 25 % to 75 % twitch height recorded.

Blood samples were obtained from the patients in the vecuronium and pancuronium groups at the end of the 15-min constant infusion–response intervals at 90 % and 50 % twitch depression, for determination of plasma concentrations of the drugs. For the vecuronium assay, 5-ml samples of whole blood were placed in test tubes containing 1 ml of KH_2PO_4 1 mol $litre^{-1}$. The blood was mixed thoroughly with the buffer, and kept at 4 °C until it was centrifuged (within 2 h). The plasma was separated and stored at −70 °C until analysis. The concentrations of vecuronium were determined by a fluorimetric technique. The method has a sensitivity of 5 ng ml^{-1}, showing a 3–10 % variation in precision in the range 5–1000 ng ml^{-1} (U. W. Kersten, in preparation). For the pancuronium assay, blood samples were collected in heparin-containing tubes (Vacutainer) and kept at 4 °C until centrifuged within 3 h. The plasma was separated and stored at −70 °C until analysis. The drug concentrations were determined by the fluorimetric method described by Kersten, Meijer and Agoston (1973).

Plasma clearance was calculated conventionally, where the rate of input by a zero-order infusion was divided by the plasma concentration at assumed steady-state.

Ringer's acetate solution was the only fluid administered during the operation. Bleeding was minimal. Lignocaine 5 mg ml^{-1} with adrenaline 5 μg ml^{-1} was injected to the operative field no later than 15 min before the constant infusion–response intervals.

Depression of twitch height was analysed statistically in probit values (Finney, 1952), and log transformation was used in the statistical analyses of dose requirements and plasma concentrations of the drugs. In the analyses of the twitch responses, the Kruskal–Wallis test or the Wilcoxon test was used, unless another method was indicated. Other statistical analyses were by Student's t test. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The three groups of patients were comparable with respect to age, weight and body surface area (table I).

Figure 1 demonstrates that there were no

TABLE I. *Characteristics of the three groups of patients (mean values ± SD)*

Drug group	n	M/F	Age (yr)	Weight (kg)	Body surface area (m^2)
Atracurium	10	1	33.9 ± 12.8	68.2 ± 13.3	1.80 ± 0.21
Vecuronium	10	1	37.8 ± 12.9	66.9 ± 9.5	1.80 ± 0.16
Pancuronium	10	1	29.0 ± 12.1	70.5 ± 6.1	1.85 ± 0.13

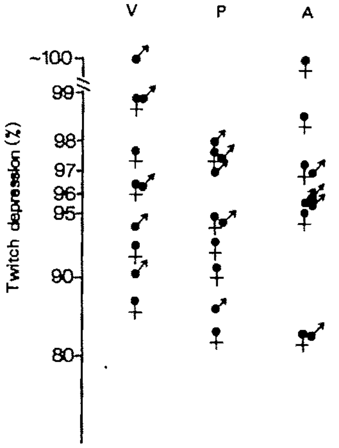

FIG. 1. Individual responses to bolus injections of estimated ED_{95} doses. V = vecuronium 56 μg kg^{-1}, P = pancuronium 64 μg kg^{-1} and A = atracurium 279 μg kg^{-1}.

differences in sensitivity to the three neuromuscular blocking drugs between men and women ($P > 0.4$ in either drug group). To test the overall sex difference, we calculated Wilcoxon test statistic for each drug group, assuming a normal approximation with continuity correction (Lehmann, 1975). By addition of χ^2-statistics (Armitage, 1980), the estimated $P = 0.56$. Because there was no indication of a sex difference in the sensitivity to the neuromuscular blockers, the stratification factor was ignored in the subsequent statistical analysis.

Single bolus injections of the previously calculated mean ED_{95} doses produced neuromuscular blockade which did not differ significantly between groups (table II). The equivalent median responses of the mean ED_{95} doses were estimated from the data of the previous cumulative dose–response study (Gramstad and Lilleaasen 1982), and quoted in table II. The cumulative dose–response technique gave a slightly more marked response for pancuronium and slightly less marked response for vecuronium, compared with equivalent single bolus injections; however, the differences were not significant. Neither were the differences significant if only female patients were compared with each other. Median bolus effects (%) with total ranges in these patients were: atracurium 97.3 (83.6–100), vecuronium 96.5 (87.5–98.9), and pancuronium 93.3 (83.7–97.7).

If we assume that the bolus dose–response relationships have slopes similar to the cumulative dose–response curves (Gramstad and Lilleaasen, 1982), the potency ratio for bolus doses producing about 95% twitch depression was 1:4.1:5.1 for atracurium, pancuronium and vecuronium, respectively.

Practically stable infusion–response conditions were obtained in all patients before we tested the change in response at fixed-rate infusion for the 15-min period. Figure 2 shows the distribution of the responses at each end of these time intervals. The individual changes in response from start to end of the constant-rate infusion are given in table III. One per cent change of control twitch height equals 0.057 probits at 90% response and 0.025 probits at 50% response. One patient in the vecuronium group was excluded from the 90% constant effect interval because of leakage from the infusion line.

The drug requirements during the 15-min intervals at 90% and 50% twitch depression are presented in table IV. Figure 3 gives a graphic presentation of the dose–response relationships

TABLE II. *Median bolus effects of mean cumulative ED_{95} doses. Equivalent median effects of the latter doses are quoted. 98% confidence intervals are given in parentheses*

	Cumulative dose–responses		
Drug	Mean ED_{95} (μg kg^{-1})	Equivalent median effect (%)	Median bolus effect (%)
Atracurium	279	95.7 (80.2–98.6)	95.8 (83.6–98.6)
Vecuronium	56	93.7 (85.8–98.9)	96.5 (90.5–98.9)
Pancuronium	64	96.3 (88.9–97.5)	94.7 (86.6–97.7)

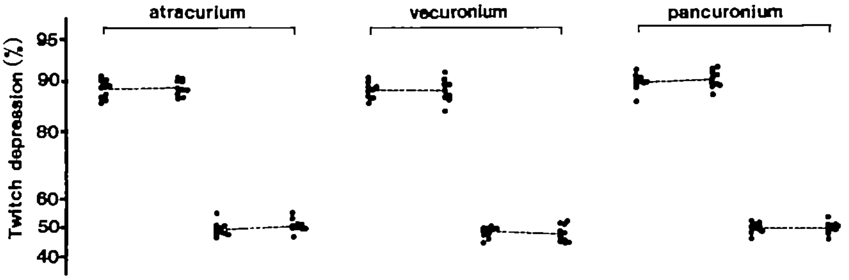

FIG. 2. Distribution of drug responses at beginning and end of the 15-min constant-rate infusion intervals. Broken lines indicate mean values.

TABLE III. *Changes in response during the 15-min constant-rate infusions. Values are probit medians with total and interquatile ranges (0.28–0.72 fractile when* n = *9)*

Drug	90%-interval (10^{-2} probits)	50%-interval (10^{-2} probits)
Atracurium	3 (2,2–10,19)	3 (1,2–4,10)
Vecuronium	2 ($n = 9$) (0,1–6,29)	6 (2,2–12,15)
Pancuronium	3 (1,2–7,14)	1 (0,1–2,3)

for the three drugs at the two levels of neuromuscular blockade. The relative dose-requirements for 90% and 50% continuous blockade were: atracurium 1.62, vecuronium 1.63 and pancuronium 1.86.

The concentrations of vecuronium and pancuronium in plasma at the end of the constant dose–response intervals (EC_{90} and EC_{50}), as well as the calculated plasma clearances of the drugs, are presented in table V. Two patients in the vecuronium group were excluded from the EC_{90} determination, because of leakage from the

TABLE IV. *Dose requirements for the maintenance of constant responses. These values are mean drug infusion rates with 95% confidence limits. The corresponding responses at the end of the constant-rate infusion periods are mean values with total ranges*

	90% response level		50% response level	
Drug	Dose ($\mu g\ kg^{-1}\ h^{-1}$)	Block (%)	Dose ($\mu g\ kg^{-1}\ h^{-1}$)	Block (%)
Atracurium	382.8 (331.0–442.7)	89.2 (86.4–90.8)	237.0 (198.6–282.8)	50.7 (46.5–55.3)
Vecuronium	101.9 ($n = 9$) (87.4–118.7)	88.6 ($n = 9$) (84.6–91.4)	62.4 (56.6–68.8)	47.7 44.5–51.9)
Pancuronium	36.9 (31.1–43.7)	90.0 (87.5–91.7)	19.8 (16.4–23.8)	49.0 (45.0–52.8)

TABLE V. *Plasma concentrations and estimated plasma clearances at the end of the constant-rate infusion periods. Values are means with 95% confidence intervals.* †*Clearance was 5.4 ml* min^{-1} kg^{-1} *(4.4–6.4) for* n = *8 (paired values with those measured at 90% response).* **Values significantly different from each other* ($P < 0.001$) *(paired* t *test)*

	90% response level		50% response level	
Drug	Concn (mg $litre^{-1}$)	Clearance (ml $min^{-1}\ kg^{-1}$)	Concn (mg $litre^{-1}$)	Clearance (ml $min^{-1}\ kg^{-1}$)
Vecuronium	0.29 ($n = 8$) (0.25–0.33)	5.9 ($n = 8$) (4.9–7.0)	0.21 (0.17–0.24)	5.2† (4.3–6.0)
Pancuronium	0.32 (0.29–0.35)	2.0* (1.6–2.4)	0.23 (0.21–0.26)	1.5* (1.1–1.8)

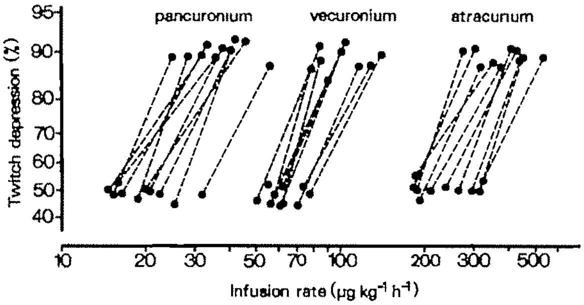

FIG. 3. Relationship between infusion rate and sustained response.

infusion line, and an unsuccessful collection of the plasma sample. The relative potencies of vecuronium and pancuronium in plasma were 1.1:1 both for 50% and 90% twitch depression.

The 25–75% recovery time was only estimated for atracurium and vecuronium, since surgery was completed in three patients in the pancuronium group before the completion of the recordings. The median neuromuscular blockade from which the drug effects declined were 94.3% and 95.1%, respectively. The mean 25–75% recovery index with standard error was significantly longer ($P < 0.05$) for atracurium (10.3 min ± 0.59) than for vecuronium (8.5 min ± 0.51).

DISCUSSION

The mean cumulative ED_{95} dose of each drug, which was calculated in a previous study (Gramstad and Lilleaasen, 1982), produced similar median responses in the three drug groups when injected as a single bolus. Median values were used for this estimation, since the bolus effect in two patients approximated 100%, for which the probit is not defined. Cumulative median responses of the mean ED_{95} doses were, therefore, also calculated from our previous study to permit relevant comparisons. The present findings confirm the previous estimation of the relative potencies of atracurium, vecuronium and pancuronium to be approximately 1:5:4. Robertson and co-workers (1983) estimated vecuronium to be 4.4 times more potent than atracurium using the cumulative technique; however, atracurium appeared slightly less potent after the bolus injection of these relative doses.

Even though the bolus responses corresponded well with those observed with the cumulative technique, the latter method tended to slightly over-estimate the potency of pancuronium and slightly under-estimate the potency of the shortest-acting drug, vecuronium.

Fisher and colleagues (1982) and Katz and co-workers (1982) found a wider discrepancy between the two techniques for the potency of vecuronium and atracurium, respectively. In our previous study, we restricted the cumulative injections to four doses. The limited time might explain the better agreement with our bolus responses. The cumulative technique might be further improved by the use of three cumulative doses for the intermediate-acting neuromuscular blockers.

An initial loading dose was given so that steady-state conditions at 90% response, during the continuous infusion, would be achieved rapidly. The optimal size of this initial bolus should not be larger than the product of the desired steady-state concentration and the apparent distribution volume (Hull, 1979). By using the data of Shanks and colleagues (1980) we estimated this maximal dose of pancuronium to be 75.4 μg kg^{-1}, which made it reasonable to select the ED_{95} (64 μg kg^{-1}) as the loading dose. Because our EC_{90} value (0.32 mg litre^{-1}) was larger than the value estimated from the data of Shanks and colleagues (1980) (0.246 mg litre^{-1}), the possibility of initially overloading the peripheral tissues was even less likely. Assuming a distribution volume for vecuronium of 252 ml kg^{-1} (Bencini et al., 1983) and $EC_{90} = 0.29$ mg litre^{-1} (present finding), the maximal suitable loading dose in our study would be 73 μg kg^{-1}, which provided a proper margin to the selected ED_{95} (56 μg kg^{-1}).

In all patients, stable 90% twitch responses were obtained before 60 min of blockade had elapsed, after which the change in response to the constant-rate infusion was minimal. During infusions producing a constant response, equilibrium with peripheral compartments approaches 95% of steady-state after four to five distribution half-lives. By evaluating the distribution kinetics of the drugs in the literature, we chose 60 min as the time after which the assumed constant infusion–response conditions were continued for a further interval. Atracurium has been shown to distribute rapidly with a half-life of 2 min (Ward et al., 1983). The distribution of vecuronium has been estimated to be slower: half-life 3.9 min (Van der Veen and Bencini, 1980), 8.5 min (Fahey et al., 1981), and 13 min (Cronnelly et al., 1983). The distribution half-life of pancuronium is reported to be 9.9 min ($\alpha = 0.07\ \text{min}^{-1}$) (Shanks et al., 1980), and 7 min (Duvaldestin, Demetriou and d'Hollander, 1982). At the end of the period required for the distribution to tissue compartments, the rate of infusion will equal the rate of elimination. A zero-order infusion will then maintain a constant plasma concentration. This accords with the minimal changes in response observed during the 15-min constant-rate infusion interval before the measurements were made. It is, therefore, reasonable to assume that our measurements at 90% response were related to steady-state conditions.

Drug requirements during the 90% twitch depression interval were ($\mu g\ kg^{-1}\ h^{-1}$): atracurium 382.8, vecuronium 101.9, and pancuronium 36.9, making the relative potency for sustained 90% block 1:3.8:10.4. The infusion rate for the maintenance of 90% response with vecuronium has previously been reported to be less. Agoston and co-workers (1980) reported values in the range of 11–87 $\mu g\ kg^{-1}\ h^{-1}$. d'Hollander and colleagues (1982) estimated the average dose requirements in an age group similar to ours to be 2747 $\mu g\ m^{-2}\ h^{-1}$, which amounts to 74 $\mu g\ kg^{-1}\ h^{-1}$ in patients with our anthropometric data. The infusion rate of pancuronium for a constant 90% decrease in twitch tension at 0.3 Hz during 0.45–0.75% halothane has been reported to be 0.135 mg m^{-2} /10 min (Miller and Eger, 1976), which would approximate 21.3 $\mu g\ kg^{-1}\ h^{-1}$ in our patient group. This may accord with the potentiation of pancuronium by the inhalation anaesthetic and the augmentation of the twitch depression at the high frequency of stimulation. d'Hollander and colleagues (1983) estimated the dose requirement of atracurium during 90% sustained blockade in patients in an age group similar to that of our patients to be 14.2 mg $m^{-2}\ h^{-1}$. This amounts to 374 $\mu g\ kg^{-1}\ h^{-1}$ in patients with our anthropometric data, and is similar to our finding.

The assays used for vecuronium and pancuronium do not differentiate between the parent drug and its metabolites. As discussed by Savage, Sleigh and Carlyle (1980), it is probable that vecuronium is primarily metabolized to its 3-deacetyl derivative. Bencini and colleagues (1983) found that only a small fraction of the total dose of vecuronium appeared in the urine and bile as the 3-OH metabolite several hours after i.v. administration. In the plasma they were unable to detect this breakdown product. Metabolites of pancuronium could not be detected in urine for at least 2 h following administration (Shanks, Somogyi and Triggs, 1979), making it probable that the breakdown products appear in low concentration in the plasma during the first few hours of an administration.

The mean plasma concentrations of vecuronium during 90% and 50% sustained blockade measured in our study (0.29 and 0.21 mg $litre^{-1}$, respectively) are greater than previously reported. Van der Veen and Bencini (1980) estimated EC_{90} and EC_{50} to be 0.206 and 0.137 mg $litre^{-1}$, respectively; and Cronnelly and co-workers (1983) estimated EC_{50} to be 0.094 mg $litre^{-1}$ during 0.5–0.7% halothane anaesthesia. Both these groups used integrated pharmacokinetic–pharmacodynamic modelling for their estimations.

The plasma clearance of vecuronium at 90% sustained block (5.9 ml $kg^{-1}\ min^{-1}$) was insignificantly larger than was estimated at 50% block (5.2 (5.4) ml $kg^{-1}\ min^{-1}$). These values are consistent with the findings of Bencini and colleagues (1983) and Cronnelly and co-workers (1983), which were 4.93 and 5.2 ml $kg^{-1}\ min^{-1}$, respectively, but are greater than those reported by Fahey and colleagues (1981) (3.0 ml $kg^{-1}\ min^{-1}$). Assuming linear pharmacokinetics for vecuronium and equal distribution volumes at the two constant-effect intervals, the insignificant difference in the plasma clearances at 90% and 50% sustained blockade, indicates that the dose requirements for the maintenance of 50% response were also closely related to the steady-state conditions.

The mean plasma concentration of pancuronium measured at 50% sustained blockade (0.23 mg $litre^{-1}$) is similar to previous findings by Shanks, Somogyi and Triggs (1979) (0.20 mg $litre^{-1}$), Hull, English and Sibbald (1980) (0.296 mg $litre^{-1}$), and Evans and co-workers (1984) (0.21 mg $litre^{-1}$). Calculated mean estimates of EC_{90} from the reported results of those papers range from 0.25 to 0.42 mg $litre^{-1}$, and are in agreement with our mean value (0.32 mg $litre^{-1}$).

Plasma clearance of pancuronium at 90% blockade was estimated to be 1.99 ml $kg^{-1}\ min^{-1}$, which is in agreement with previous findings of 2.11 ml $kg^{-1}\ min^{-1}$ (Somogyi, Shanks and Triggs, 1978), 1.76 ml $kg^{-1}\ min^{-1}$ (Miller et al., 1978), and 1.84 ml $kg^{-1}\ min^{-1}$ (Duvaldestin, Demetriou and d'Hollander, 1982).

At the later 50% blockade the estimated plasma clearance was significantly smaller. The pharmacokinetics of pancuronium have been shown to be linear (Duvaldestin, Demetriou and d'Hollander, 1982) and, when assuming that the volume of distribution remained constant, this reduction in the estimated plasma clearance can be explained by a continuous transfer of drug from peripheral tissues to plasma, even at 45 min infusion time with 50% sustained blockade. This invalidates our estimation of the dose requirement of pancuronium for the maintenance of 50% response.

The plasma concentrations of atracurium were not measured, as an assay technique was not readily available, and prolonged sample storage was not attempted because of possible *in vitro* degradation. The major route of inactivation of atracurium is by "Hofmann elimination", and degradation will also take place in peripheral tissues (Ward et al., 1983). This makes it unlikely that significant transfer of drug from peripheral tissues to plasma would occur when establishing the 50% response. Moreover, the short distribution half-life makes it reasonable to assume that steady-state conditions will be attained rapidly during the constant response infusion. The drug requirements of both atracurium and vecuronium at 90% and 50% sustained blockade can thereby be adequately compared.

The relative maintenance doses for 90% and 50% sustained blockade were found to be: atracurium 1.62 and vecuronium 1.63. From the results in the previous cumulative dose–response study we found the relative dose requirements for the initial blockade to be 1.64 and 1.62, respectively, for the same response interval. This implies that the same relative increase in dose is required from 50% to 90% blockade for the induction as well as the maintenance of neuromuscular blockade with atracurium and vecuronium.

The recovery rate from 25% to 75% twitch height was significantly shorter for vecuronium than for atracurium, when recovering from about 95% twitch depression. Robertson and co-workers (1983) observed significantly shorter recovery after vecuronium than atracurium after giving ED_{90} doses, but no difference after $3 \times ED_{90}$ doses. They suggested that the prolonged recovery might be the result of saturation of the distribution volume at the higher dose. Estimations of the 25–75% recovery index for atracurium have given consistently similar results in different studies and with different doses (Basta et al., 1982; Robertson et al., 1983).

In conclusion, our study confirms that the relative potencies for initial blockade with atracurium, vecuronium and pancuronium are approximately 1:5:4. The relative dose requirements for sustained neuromuscular blockade were 10.4:3.8:1, respectively, for 90% neuromuscular blockade. The same dose ratio also applied to sustained 50% blockade for atracurium and vecuronium. The relative potency of vecuronium and pancuronium in plasma was 1.1:1.

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COMPARISON OF CUMULATIVE AND SINGLE BOLUS DOSE TECHNIQUES FOR DETERMINING THE POTENCY OF VECURONIUM

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SUMMARY

The potency of vecuronium was determined using single bolus dose administrations of 10–50 µg kg^{-1} in 28 patients anaesthetized with thiopentone, nitrous oxide, oxygen and fentanyl. The results were compared with those previously obtained using a cumulative dose technique in a comparable group of 10 patients. The 50% and 95% blocking doses (ED_{50} and ED_{95}) of vecuronium were found to be 23.1 and 39.6 µg kg^{-1}, respectively. These were significantly lower than the 30.5 and 56.7 µg kg^{-1} obtained previously using the cumulative dose technique. We recommend the use of single bolus dose method of determining potency for relatively shorter-acting drugs like vecuronium.

Vecuronium, a recently introduced, relatively shorter-acting monoquaternary analogue of pancuronium, is considered to be almost equipotent to pancuronium (Gramstad and Lilleaasen, 1982; Ferres et al., 1984) when the potency is determined using a cumulative dose technique. Although the potency of longer-acting agents such as pancuronium and tubocurarine, as judged by the 95% blocking dose (ED_{95}), has been shown to be similar using either single bolus or cumulative dose techniques (Donlon et al., 1980), this has not been determined for vecuronium. Fisher and his colleagues (1982) showed that vecuronium was more potent when assessed by the single bolus dose technique in comparison with a cumulative dose technique; however, these workers did not provide any information on the traditionally used index of ED_{95} and, in addition, were using halothane anaesthesia, which in itself could affect the potency of vecuronium. In the present study, the potency of vecuronium has been determined using a single bolus dose method and the results compared with our previously published results (Ferres et al., 1984) using a cumulative dose method.

PATIENTS AND METHODS

The study was carried out in 28 adult patients conforming to ASA grade I, who were to undergo elective surgery for repair of retinal detachments or follow-up surgery for trauma to the eye. All patients gave informed consent and the investigation was approved by the regional ethics committee. The anaesthetic technique and the method of studying neuromuscular transmission were exactly the same as in our previous study using the cumulative dose technique (Ferres et al., 1984).

Following premedication with diazepam 10–15 mg by mouth, anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and maintained with 66% nitrous oxide, and fentanyl 4–5 µg kg^{-1}. Additional increments of fentanyl 25–50 µg kg^{-1} or thiopentone 50–75 mg were administered before giving vecuronium if required. The ulnar nerve was stimulated at the wrist with supramaximal stimuli of 0.2 ms duration at 0.1 Hz using surface electrodes, the resultant force of thumb adduction being recorded on a neuromuscular function analyser (Viby-Mogensen, 1982).

Following stabilization of the control twitch height for at least 10 min, patients were randomly allocated to receive vecuronium in doses of 10 ($n = 4$), 20 ($n = 6$), 30 ($n = 6$), 40 ($n = 6$) or 50 µg kg^{-1} ($n = 6$) as a single bolus. The maximal

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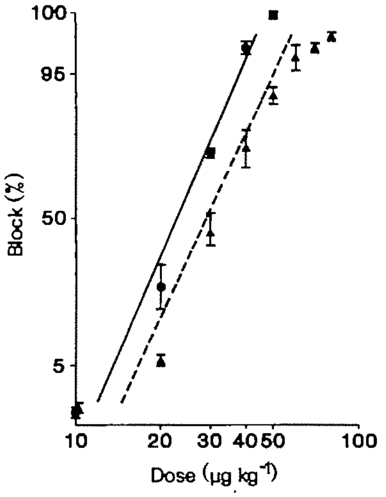

FIG. 1. Dose–response curves using the single bolus and cumulative dose techniques. Each point represents mean ± SEM. (The line for cumulative dose technique is based on the data from Ferres and colleagues (1984).)

depression in twitch height obtained in each patient was recorded.

An arc–sine transformation of the data relating to twitch height was carried out, as suggested by Armitage (1971) for responses involving the extremes (0 and 100%) on the dose–response curve. A linear regression analysis was carried out using the method of least squares, and the dose–response curve constructed. This was compared with the curve obtained previously using the cumulative dose technique. The calculated values of ED_{50} and ED_{95} with the two techniques were tested for statistical difference from each other using a Student's *t* test.

RESULTS

The patients in the present study were comparable to those in the previously reported study using the cumulative dose method (table I). The dose–response line from the present study and that obtained using the cumulative dose technique (Ferres et al., 1984) are shown in figure 1. The slopes of the two curves did not differ from each other, but the one produced using the single bolus dose method was to the left of that produced using the cumulative dose method, indicating the higher potency of the drug when the single bolus dose method was used. The ED_{50} and ED_{95} of vecuronium were 23.1 and 39.6 μg kg^{-1}, respectively, with the single bolus dose technique in comparison with 30.5 and 56.7 μg kg^{-1}, respectively, using the cumulative dose method (table I). The differences were significant ($P < 0.05$) for each end point.

TABLE I. *ED_{50} and ED_{95} of vecuronium by cumulative dose and single dose methods. †From Ferres and colleagues (1984). *Significantly different from cumulative dose method* ($P < 0.05$). *Figures in parentheses are 95% confidence intervals*

	Cumulative dose† method	Single bolus dose method
Age (yr) (mean ± SEM)	33 ± 1.8	38 ± 1.3
Weight (kg) (mean ± SEM)	59 ± 1.4	67 ± 1.6
ED_{50} (μg kg^{-1})	30.5 (24.4–36.7)	23.1* (20.6–26.0)
ED_{95} (μg kg^{-1})	56.7 (41.0–72.5)	39.6* (35.7–43.1)

The time taken to attain the maximum effect of each bolus dose varied with the size of the dose, ranging from an average of 6.7 min following a 20-μg kg^{-1} dose to 4.5 min following a 50-μg kg^{-1} dose, 10 μg kg^{-1} producing a block of 7% in only one patient.

DISCUSSION

A cumulative dose technique is preferred to a single bolus dose technique for determining the potency of neuromuscular blocking drugs, since the method requires fewer patients. The potency of drugs like pancuronium and tubocurarine is similar with the two methods (Donlon et al., 1980); however, the results from the present study clearly demonstrate that the method of determining potency of relatively shorter-acting agents like vecuronium influences the results, the single bolus dose technique giving a higher potency. The conclusions agree with those of Fisher and his colleagues (1982) who demonstrated similarly that vecuronium was more potent when the single bolus dose method of estimating potency was used. Only the ED_{50} obtained by us can be compared with their findings, since they did not give any figures for ED_{95}. The ED_{50} values as obtained by Fisher and co-workers (1982) by both methods are lower than those obtained by us, but they were using halothane anaesthesia throughout, which has been shown to increase the potency of vecuronium (Foldes, Bencini and Newton, 1980). Katz and his colleagues (1982) showed similar results for atracurium, another relatively shorter acting agent, when they found that a dose of 0.25 mg kg^{-1} produced a 95% or greater blockade when used as a single bolus in comparison with an average block of only 70% when the same total dose was administered in the form of smaller increments. Our own results with atracurium (Gibson et al., 1985) confirmed these findings.

The main reason for the difference in the results with the two techniques must lie in the shorter duration of action of vecuronium, particularly with the smaller doses used in incremental dose–response studies, significant recovery occurring before the next increment is administered, since this could sometimes be as long as 10–12 min (Fahey et al., 1981; Fisher et al., 1982). In the cumulative method, the next increment of the neuromuscular blocker is administered whenever the three successive twitches are of similar height (Donlon, Ali and Savarese, 1974) following the previous increment. It is possible that the maximum effect of the drug may not be apparent with the low doses of a drug like vecuronium for as long as an average of 6.7 min after a dose of 10 μg kg^{-1} (Fahey et al., 1981). This was borne out in the present study as well, in which a 20-μg kg^{-1} bolus produced its maximal effect in over 6.5 min.

In conclusion, the potency of vecuronium is greater when estimated by the single bolus dose technique. Since most anaesthetists administer neuromuscular blocking drugs as a bolus, it is suggested that this technique be used for assessing potency of agents like vecuronium. We further support the suggestion made by Fisher and his colleagues (1982) not to use cumulative dose–response techniques for determining potency of medium- and short-acting agents such as vecuronium and atracuium. If a cumulative dose–response technique is used, it is suggested that a larger initial dose followed by fewer and larger increments be used to minimize the effect of the time factor.

NOTE ADDED IN PROOF: Since the submission of this paper, a similar study, with similar conclusions, has been published (Ørding, H., Skovgaard, L. T., Engbaek, J. and Viby-Mogensen, J. (1985). Dose–response curves for vecuronium during halothane and neurolept anaesthesia: Single bolus versus cumulative method. *Acta Anaesthesiol. Scand.*, **29**, 121.)

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INTERACTION BETWEEN PANCURONIUM BROMIDE AND VECURONIUM BROMIDE

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SUMMARY

The interaction between two non-depolarizing neuromuscular blocking agents, pancuronium bromide and vecuronium bromide, has been studied at standardized levels of neuromuscular blockade and alternating the sequence of their administration, in 40 surgical patients. The drug administered first appeared invariably to play a dominant role in influencing both the dose requirements and the duration of action of the subsequent neuromuscular blocker. This resulted in reduced dose requirements and significant prolongation of action of vecuronium administered after pancuronium and increased dose requirements and shortening of neuromuscular blocking action of pancuronium given during vecuronium-induced partial neuromuscular blockade. Possible mechanisms of such interaction are discussed.

Vecuronium is a non-depolarizing neuromuscular blocking agent which has recently been introduced to clinical practice. Although closely related chemically to its bisquaternary analogue, pancuronium, it has a considerably shorter duration of action and lacks the occasional undesirable cardiovascular side-effects of pancuronium (Agoston et al., 1980; Crul and Booij, 1980). These differences in clinical characterstics might confer some advantage in combining the two drugs in clinical practice: the alternate administration of neuromuscular blockers with different durations of action might enable the anaesthetist to regulate to a finer degree the depth and duration of neuromuscular blockade during surgery, according to the stage of an operation and the clinical requirements. One possible application of such a combination of myoneural blockers with different durations of actions could be the administration of the shorter-acting drug for the closure of the peritoneum at the end of an abdominal operation. On the other hand, when a non-depolarizing agent is used, instead of suxamethonium, to provide blockade for intubation of the trachea, a shorter-acting drug like vecuronium, devoid of undesirable cardiovascular side effects, may be preferred. In such instances (dependent on the anticipated duration of the operation) the maintenance of blockade during surgery might be achieved using either the same drug or a longer acting compound, such as pancuronium.

We investigated the practicability of such a technique, in a study of the possible interactions between pancuronium and vecuronium. Two alternative sequences of administration of the compounds were investigated: pancuronium followed by vecuronium, and *vice versa*.

PATIENTS AND METHODS

Forty adult surgical patients of either sex (ASA I or II) were studied after informed consent had been obtained from each. Premedication consisted of papaveretum 10–15 mg and atropine 0.5 mg given i.m. approximately 1 h before the start of anaesthesia. Anaesthesia was induced with droperidol 10–15 mg, fentanyl 0.4–0.6 mg and a "sleep dose" of thiopentone. The patients' lungs were ventilated with a mixture of 67% nitrous oxide in oxygen. Small increments of fentanyl (0.05–0.1 mg) were administered as needed for the maintenance of anaesthesia.

Neuromuscular transmission was monitored continuously throughout the investigation by means of registration of the isometric twitch tension of the adductor pollicis muscle in response to indirect stimulation of the ulnar nerve at the wrist with square-wave supramaximal electrical stimuli of 0.2 ms duration at a rate of 0.1 Hz.

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TABLE I. *Combinations of neuromuscular blocking agents studied*

Group	No. patients	Blockers administered for 95% blockade		Recovery at time of injection of second drug (%)
		First drug	Second drug	
I	5	Pancuronium	Pancuronium	25
II	5	Pancuronium	Pancuronium	50
III	5	Pancuronium	Vecuronium	25
IV	5	Pancuronium	Vecuronium	50
V	5	Vecuronium	Vecuronium	25
VI	5	Vecuronium	Vecuronium	50
VII	5	Vecuronium	Pancuronium	25
VIII	5	Vecuronium	Pancuronium	50

After the induction of anaesthesia and a control recording of the twitch tension, the first neuromuscular blocking drug was injected, in increments, to a fast running infusion until approximately 95% blockade was obtained. The trachea was then intubated.

By random allocation to groups, 20 patients (five in each of groups I–IV) received pancuronium as the first neuromuscular blocker administered, and another 20 patients (five in each of groups V–VIII) received vecuronium first. Table I shows the combinations of drugs studied subsequently: neuromuscular blockade was maintained during surgery using either the same drug as for initial blockade (groups I, II and V, VI) or the alternative drug (groups III, IV and VII, VIII), administered in increments at 25% or 50% recovery after the first drug, until a blockade of 95% was again obtained. The size of the increments was determined individually in each patient, according to the effect obtained, and with the aim of achieving the desired degree of blockade (95%) with the minimal number of increments in the shortest possible time. After this the blockade was allowed to recover spontaneously.

The doses of pancuronium and vecuronium required for 95% neuromuscular blockade as well as their time course of action (clinical duration and recovery index) were compared.

Statistical analysis was with Student's t test. Differences were considered significant at $P < 0.05$.

RESULTS

Figure 1 shows the mean values of the maintenance doses of pancuronium and vecuronium required, for reinforcement of the blockade to 95% suppression of twitch height, given at 25% and at 50% recovery of the neuromuscular blockade induced by the initial dose of pancuronium or vecuronium.

At both stages of recovery after vecuronium the same magnitude of block could be produced only by using 35–40% larger maintenance doses, of either neuromuscular blocker, than were necessary after pancuronium. Understandably, at the more advanced (50%) stage of recovery from the initial

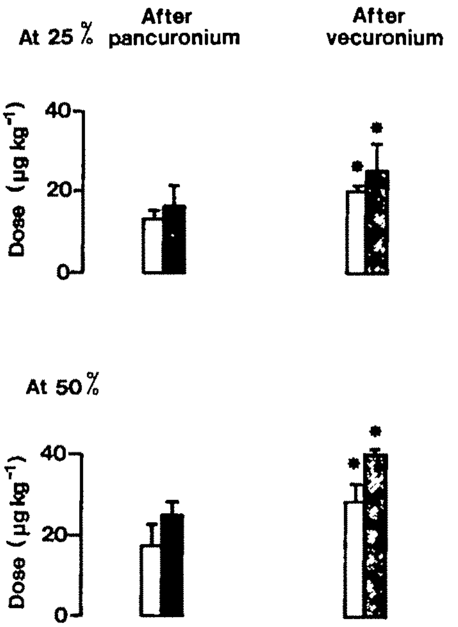

FIG. 1. Maintenance doses (μg kg⁻¹) of vecuronium (open columns) and pancuronium (cross-hatched columns) required for production of approximately 95% blockade at 25% or 50% recovery from an initial block produced by pancuronium or by vecuronium. Mean values ± SD. *Significantly different from the corresponding value after pancuronium.

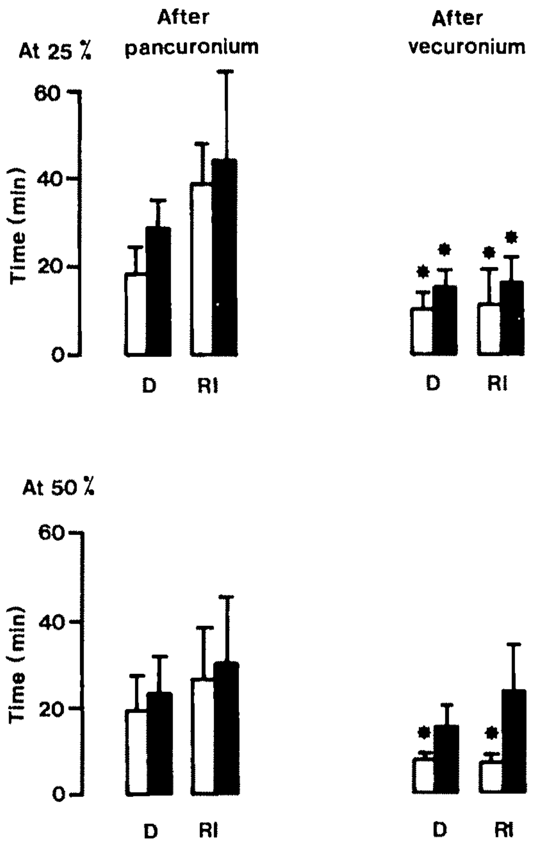

FIG. 2. Duration (min) to 25% recovery (D) and recovery indices (RI) of maintenance doses of vecuronium (open columns) and pancuronium (cross-hatched columns) administered at 25% or 50% recovery from an initial block induced by pancuronium or vecuronium. Mean values ± SD. *Significantly different from the corresponding value after pancuronium.

blockade it was necessary to use larger maintenance doses of either blocker.

It can be seen from figure 1 that, in all circumstances investigated, the dose requirements for pancuronium were 15–20% larger than the corresponding dose requirements for vecuronium. This can probably be attributed to the difference in the relative potency of the two compounds.

Figure 2 illustrates the duration of action of the maintenance doses of both drugs after pancuronium and after vecuronium, expressed as duration to 25% twitch height recovery and recovery index (duration from 25% to 75% recovery). There was a marked difference in the action of both drugs according to which neuromuscular blocker was administered first: after pancuronium *both* drugs were effective for significantly longer than after vecuronium. This difference was especially pronounced when the drugs were given at the less advanced stage of recovery (25%). Although the duration of action of pancuronium was always longer than that of the comparable dose of vecuronium, the differences (expressed as a percentage of the greater value in the pair) between comparable clinical durations and recovery indices observed after administration of the same initial blocker were not great, with the exception of drugs given at 50% recovery after vecuronium.

DISCUSSION

Since the introduction of neuromuscular blocking drugs to anaesthesia, attempts have been made to use their different properties to advantage by combining them in clinical practice. Such combined use, however, has had only limited clinical application because the interactions between different blockers remain one of the least investigated problems in modern anaesthesia.

Theoretically, the administration of two drugs, such as non-depolarizing neuromuscular blockers, which affect the same primary sites of action similarly, should result in a summation of their separate effects (addition). However, this proved not always to be true. It has been shown, in both clinical and experimental studies, that, while concomitant administration of some mixtures of non-depolarizing neuromuscular blocking agents (pancuronium–alcuronium; tubocurarine–dimethylcurarine (metocurine); pancuronium–vecuronium) does result in additive action, other mixtures of non-depolarizing blockers (tubocurarine with gallamine, alcuronium, pancuronium or vecuronium; metocurine–pancuronium) clearly demonstrate synergistic (super-additive), rather than additive, effects (Wong, 1969; Ghoneim et al., 1972; Lebowitz et al., 1980; Ferres et al., 1983; Pollard and Jones, 1983; Gibson et al., 1984). These observations may be interpreted as indicating that combinations of structurally similar compounds exert only an additive action, while combinations of structurally dissimilar substances produce a potentiating response, the latter effect reflecting different mechanisms of action of structurally dissimilar substances acting at pre- and postsynaptic, and possibly other, binding sites in the neuromuscular junction.

The studies referred to above were carried out using concomitant administration of different non-depolarizing agents. The present study has clearly demonstrated that the results of the consecutive administration of such drugs depend on the sequence of their administration: after administration of pancuronium first, the maintenance dose requirements for pancuronium or for vecuronium were smaller, and the duration of blockade longer, than after administration of vecuronium first. The drug administered first obviously played a dominant role, and exerted a determining influence on both the dose and the duration of action of the blocking agent subsequently given.

According to Paton and Waud (1967), the "margin of safety" of neuromuscular transmission accounts for 75–80% of all receptors, which must be blocked before there is any decrease in the twitch response. This means that, at 25% or 50% twitch height recovery from the initial blockade, when the blockade is reinforced by the second drug, the great majority of the receptors are still occupied by the first drug. Consequently, the resulting summation of the effects of both drugs reflects mainly the effect of the first drug and, to a lesser extent, that of the second. This would explain the apparent prolongation of the action of a maintenance dose of (otherwise short-acting) vecuronium following initial blockade by (longer-acting) pancuronium and a blockade of short duration following a maintenance dose of pancuronium after initial blockade by vecuronium.

It is generally believed that the plasma clearance rate is an important factor in determining the duration of action of a muscle relaxant. Drugs that leave the plasma more rapidly have shorter durations of action, and *vice versa*. It is conceivable that the dose requirement for a drug subsequently given would depend on the plasma clearance rate of the one previously given: a drug with faster clearance will thus impose the requirement for a larger maintenance dose of any drug by which it is substituted than would a drug with a slower clearance. The total plasma clearance rate of vecuronium was shown to be three to five times greater than that for pancuronium (Bencini, 1982), which would thus explain the reduced maintenance dose requirements for both compounds after pancuronium, and the increased dose requirements after vecuronium.

CONCLUSIONS

Administration of the "short-acting" neuromuscular blocking drug, vecuronium, with the aim of providing blockade of short duration in the final stages of an operation after pancuronium has been given earlier seems unjustified, since significant prolongation of the recovery, resembling the pattern of recovery from pancuronium, will ensue.

When pancuronium is considered for administration to maintain neuromuscular blockade after the initial use of vecuronium, it should be realized that the desired degree of neuromuscular blockade would require an increased dose of pancuronium, and that its duration might be much shorter than expected.

When using different non-depolarizing muscle relaxants in the course of anaesthesia, the anaesthetist should be aware of the possibility of interactions (sometimes unpredictable) between them, which depend not only on the specific drugs used, but also on the sequence of their administration. Monitoring of neuromuscular transmission in such instances is, therefore, advisable.

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A COMPARISON OF ATRACURIUM AND ALCURONIUM DURING HALOTHANE ANAESTHESIA BY MEASUREMENT OF THE TRAIN-OF-FOUR RESPONSE OF THE ADDUCTOR POLLICIS MUSCLE AND CLINICAL OBSERVATION

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SUMMARY

Atracurium and alcuronium have been compared during halothane anaesthesia, by measurement of the mechanical response of the adductor pollicis muscles to train-of-four stimulation and by clinical observation. Atracurium appeared significantly shorter-acting than alcuronium. However, results suggested that the action of alcuronium may not be of "medium duration". A comparison of three indices of muscle twitch response to the train-of-four nerve stimulation, seemed to indicate that the D′/D ratio gave the best overall index of neuromuscular blockade in this study.

Atracurium besylate is a new non-depolarizing neuromuscular blocking agent which has been extensively studied and its effect compared with those of other neuromuscular blocking agents (Payne and Hughes, 1981; Foldes et al., 1983; Gramstad, Lilleaasen and Minsaas, 1983; Twohig, Ward and Corall, 1983).

Atracurium undergoes spontaneous degradation under physiological conditions by "Hoffmann elimination" and, to a lesser extent, ester hydrolysis (Stenlake et al., 1983). Consequently, it has a shorter duration of action and better reversal characteristics than most other neuromuscular blockers.

Alcuronium chloride is a non-depolarizing neuromuscular blocking agent which has been in use for some 20 years (Lund and Stovner, 1962a, b; Bush, 1964). It has been described as having an action of "medium duration" (Hunter, 1964; Russell-Jones and Keating, 1964). Although there have been comparative studies with other non-depolarizing blockers (Bush, 1965; Baraka, 1967; Lund and Stovner, 1969; Pandit, Dundee and Stephenson, 1971) only one comparative study has been carried out in recent years with a drug of intermediate duration — vecuronium (Kreig, Crul and Booij, 1980).

The impression of the medium duration of action of alcuronium is based largely on clinical observation. For this reason, the neuromuscular pharmacology of these two drugs was compared by both measurement of mechanical muscle twitch in response to nerve stimulation, and clinical observation.

PATIENTS AND METHODS

Forty healthy women (ASA class 1), admitted for gynaecological surgery, gave informed consent for the study. All were premedicated with pethidine 1–1.5 mg kg^{-1} i.m. and atropine 0.6 mg i.m. approximately 1 h before surgery. Anaesthesia was induced with thiopentone 3.5–6 mg kg^{-1} i.v. and maintained with 60–66% nitrous oxide and 0.5% halothane in oxygen. Supplements of thiopentone 25 mg were given as needed during the setting up of the nerve stimulator and recording device, and whilst stable recordings were being obtained.

The ulnar nerve was stimulated at the wrist using a Dupaco (Model 54120) nerve stimulator.

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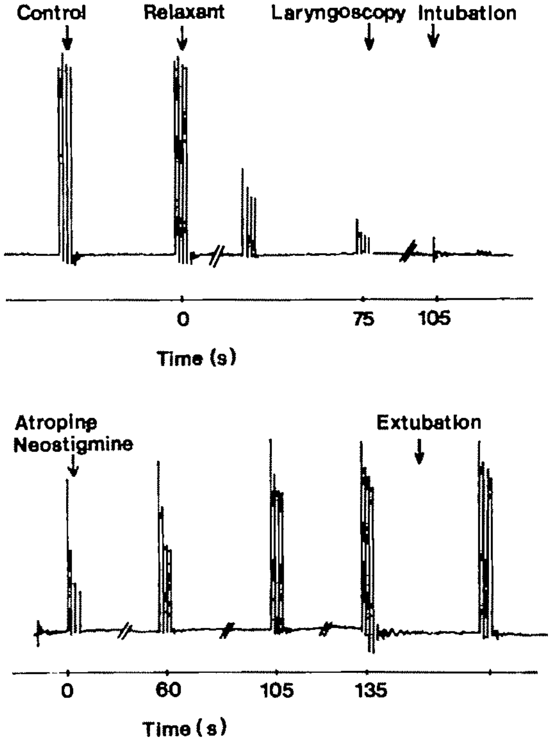

FIG. 1. Typical recording ot train-of-four twitch response of adductor pollicis following atracurium 0.5 mg kg^{-1} i.v. and atropine 1.2 mg with neostigmine 2.5 mg i.v.

TABLE I. *Signs used to assess conditions for tracheal intubation. A score of 5 indicated ideal conditions*

Clinical signs for intubation	Score	
	Present	Absent
Jaw tone	0	1
Swallowing	0	1
Cord movement	0	1
Bucking	0	1
Bronchospasm	0	1

TABLE II. *Signs used to assess recovery from neuromuscular blockade to permit tracheal extubation. A maximum score of 5 was considered ideal*

Clinical signs for extubation	Score	
	Present	Absent
Breathing ($V_T > 7$ ml kg^{-1})	1	0
Swallowing	1	0
Bucking or coughing	1	0
Inspiration force > 10 cm H_2O	1	0
Head raising on command	1	0

Supramaximal stimuli were delivered percutaneously via 25-gauge needle electrodes. Comparison of the fourth twitch (T4) in a train of four (TOF) sequence with T4 in the TOF sequence under control conditions, was considered to provide a suitable assessment of neuromuscular blockade (Lee, Barnes and Katz, 1976). Evoked adductor pollicis twitch tension was measured by means of a force displacement device, consisting of a spring-loaded plastic syringe, connected to a Statham P23Db pressure transducer, and recordings were made on a Gould–Bryan polygraph. A typical recording is shown in figure 1.

After stable control values of TOF twitch response had been obtained, patients were randomly allocated to receive either atracurium 0.5 mg kg^{-1}, or alcuronium 0.25 mg kg^{-1}. Intubation of the trachea was performed when 90% depression of T4 was observed, and intubating conditions were graded on the basis of five clinical observations (table I).

Anaesthesia was maintained with 60–66% nitrous oxide and 0.5% halothane in oxygen supplemented with pethidine 20–30 mg i.v. as required. Increments of neuromuscular blocker, one-third of the loading dose, were administered when indicated by diaphragmatic activity or increased muscle tone, irrespective of the observed twitch response.

The minute volume of ventilation was adjusted to give an end-tidal carbon dioxide concentration between 4 and 5 kPa as measured on a Puritan–Bennett Datex infra-red end-tidal carbon dioxide monitor. In addition, samples of arterialized venous blood were taken at intervals for blood-gas analysis and for estimation of acid–base balance. At the end of each procedure, neostigmine 2.5 mg and atropine 1.2 mg i.v. were given if the recovery of the fourth twitch (T4) of TOF, was less than 75% of the control value. Immediately before extubation, a clinical assessment of the patient's neuromuscular status was made (table II).

Observation of the patient was continued following extubation. Patients were judged fully recovered when they fulfilled the five clinical criteria indicated in table III. The time from extubation to "full recovery" was noted.

All TOF twitch response recordings were analysed, and three indices of TOF were compared to determine which demonstrated the best assessment of neuromuscular blockade (fig. 2).

TABLE III. *Criteria used in the recovery room to indicate clinical recovery from neuromuscular blockade*

(1) Minute volume $\geqslant 9$ ml kg^{-1} min^{-1}
(2) Inspiration force 20 cm H_2O
(3) Explosive cough present
(4) Sustained head lift $\geqslant 5$ s
(5) Absence of diplopia

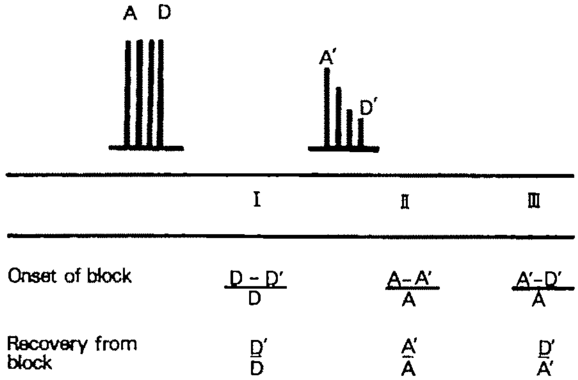

FIG. 2. I–III were the three parameters of TOF compared during onset of and recovery from neuromuscular block. Parameter I formed the basis of the twitch studies in this investigation.

Statistical analysis of the results obtained was performed using the Student *t* test, regression of least squares, Wilcoxon rank sum test (unpaired), or the Chi squared test, where appropriate. Statistical significance was set at a probability value of $P < 0.05$.

RESULTS

Both groups of patients were comparable with regard to age and weight (table IV).

TABLE IV. *The mean age and weight of the patients, and the numbers* (n) *randomly assigned to receive either atracurium 0.5 mg kg*$^{-1}$ *or alcuronium 0.25 mg kg*$^{-1}$

Group	Patient *n*	Mean age (yr ± SEM)	Mean weight (kg ± SEM)
Atracurium	20	34.25 ± 7.6	64.8 ± 11.7
Alcuronium	20	38.65 ± 7.5	63.2 ± 11.6

Onset of neuromuscular blockade and conditions on intubation

TABLE V. *The onset of neuromuscular blockade and the time (mean ± SEM) required to perform intubation in both groups*

Group	Time to 90% depression T4 (s)	Time to tracheal intubation (s)	T4 depression at intubation (%)
Atracurium	116.1 ± 6.7	143.8 ± 7.9	95.9 ± 0.5
Alcuronium	136.6 ± 11.3	164.7 ± 11.8	94.5 ± 0.5

The onset time of neuromuscular blockade was the time from injection of the drug to 90% depression of T4. Table V shows that atracurium exhibited a more rapid rate of onset than alcuronium, but the difference between the two was not statistically significant.

The time to intubation in the atracurium group was also shorter, but not significantly so. T4 twitch height depression at intubation with alcuronium was slightly, but not significantly less than that in the atracurium group.

The clinical intubation scores awarded to the patients in the two groups are shown in table VI. Statistical analysis revealed no significant differences. Within each group there was no correlation between the clinical intubation score and depression of T4 at intubation.

The maximum depression of T4 and the number of patients achieving 100% neuromuscular blockade were similar in both groups (table VII).

The T4 recovery period from maximum blockade to 10% of control twitch height was significantly shorter in the atracurium group, as were the recovery periods to 50% and 70% of control twitch height. Recovery of twitch height to 75% or more of control within the duration of surgical anaesthesia was not observed in any patient who had received alcuronium (fig. 3).

Duration of anaesthesia was similar in both groups of patients, but more increments of neuromuscular blocker were required by patients who received atracurium (table VIII).

TABLE VI. *The distribution of clinical intubation scores given to patients in both groups, and the number of patients in each category.* $\chi^2 = 7.77$; $P > 0.5$

Group	Clinical intubation score achieved 1	2	3	4	5	Total No. patients
Atracurium	0	1	2	10	7	20
Alcuronium	1	2	6	9	2	20

TABLE VII. *Maximal neuromuscular blockade achieved in the two groups of patients*

Group	Maximum T4 depression (% ± SEM)	Patients with 100% depression T4 (%)
Atracurium	99.76 ± 0.12	85
Alcuronium	99.76 ± 0.13	75

TABLE VIII. *Number of patients receiving one, two or three incremental doses of blocker required on clinical grounds and the duration of anaesthesia*

Group	No. of increments given			Duration of anaesthesia (min ± SEM)
	1	2	3	
Atracurium	16	5	3	97.52 ± 6.44
Alcuronium	1	0	0	86.2 ± 6.35

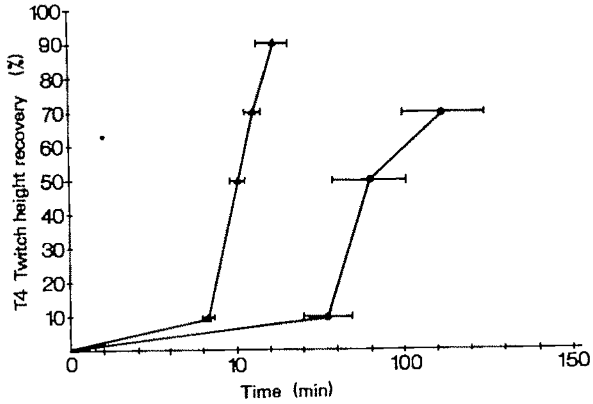

FIG. 3. Onset, duration and reversal of neuromuscular blockade in 20 patients receiving atracurium 0.5 mg kg^{-1} (▲), and 20 patients receiving alcuronium 0.25 mg kg^{-1} (●): percent change in T4 twitch height over control (recovery) plotted against time. Horizontal lines indicate SEM.

Reversal of neuromuscular blockade

Within the atracurium group, the time interval from the last increment of the blocker to the end of the surgical procedure, was significantly different between those patients who required neostigmine and those who did not.

All patients receiving alcuronium required neostigmine, compared with only 13 of the patients who had received atracurium. However, following the administration of neostigmine the degree of reversal of neuromuscular blockade was comparable in both groups. There was no significant difference between any group, whether or not neostigmine was required, in the time interval from reversal or cessation of anaesthesia to extubation (table IX).

Extubation and recovery following extubation

At extubation, patients in the atracurium group who did not need neostigmine had a significantly greater degree of recovery of the T4 twitch height. The time taken to reach full "clinical" recovery, however, was similar in all patients for up to 2 h into the post-extubation period (table X).

Table XI shows the distribution of clinical extubation scores assigned to patients. There was no significant difference in the scores allocated. Within each group there was no significant correlation between the clinical extubation score and T4 recovery at extubation.

On comparison of the three indices of TOF, I was found to be the most sensitive index of neuromuscular blockade during onset, whilst III appeared to be the least sensitive. However, both I and III seemed to be equally sensitive indices of

TABLE IX. *The effect of neostigmine in both groups, and the twitch height changes observed from cessation of anaesthesia to extubation in patients not requiring neostigmine.* n = *Number of patients.* *$P < 0.001$*; † < 0.001 compared with top line*

	Neostigmine reversal of block	Time from last increment to reversal (min ± SEM)	T4 twitch height at reversal (% ± SEM)	T4 twitch height increase from reversal to extubation (% ± SEM)	Time from reversal to extubation (s ± SEM)
Atracurium	Yes ($n = 13$)	24.42 ± 2.63	19.26 ± 5.03	48.1 ± 8.2	303.62 ± 65.45
Atracurium	No ($n = 7$)	67.57 ± 8.17†	93.84 ± 2.01	2.72 ± 1.06	351.29 ± 86.34
Alcuronium	Yes ($n = 20$)	88.05 ± 5.91*	22.10 ± 5.64	45.77 ± 4.33	283.5 ± 24.03

TABLE X. *The T4 twitch recovery at extubation and the time taken to reach "full" recovery from neuromuscular blockade.* n = *Number of patients*

Group	Neostigmine reversal of block	T4 twitch recovery at extubation (% ± SEM)	Time from extubation to full recovery (min ± SEM)
Atracurium	Yes	67.36 ± 7.24 (*n* = 13)	15.83 ± 2.11 (*n* = 12)
Atracurium	No	96.56 ± 1.82 (*n* = 7)	10.0 ± 3.24 (*n* = 4)
Alcuronium	Yes	67.87 ± 5.43 (*n* = 20)	17.83 ± 2.06 (*n* = 12)

TABLE XI. *The distribution of clinical scores assigned to patients in both groups, and the numbers of patients falling within each category.* $\chi^2 = 0$; P = *1.0*

Group	Clinical extubation scores achieved 1	2	3	4	5	Total No. of patients
Atracurium	0	0	0	10	10	20
Alcuronium	0	0	0	10	10	20

TABLE XII. *Train-of-four indices I–III (see figure 3) were compared during onset of neuromuscular block at 90% depression of control twitch height, during recovery from neuromuscular block at 50% of control twitch height, and at time of neostigmine reversal*

TOF indices	90% Depression of control twitch T4 (% ± SEM	T4 twitch height at reversal (% ± SEM)	T4 twitch recovery at 50% of control (% ± SEM)
Atracurium			
I	91.17 ± 0.38	19.26 ± 5.03	50.79 ± 0.86
II	72.8 ± 1.47	54.18 ± 9.72	97.17 ± 1.07
III	66.4 ± 1.87	20.61 ± 5.65	50.82 ± 1.84
Alcuronium			
I	90.7 ± 0.22	22.01 ± 5.64	49.96 ± 1.39
II	82.35 ± 1.31	69.17 ± 7.13	95.32 ± 2.14
III	50.66 ± 1.97	23.03 ± 5.09	50.01 ± 0.82

recovery from neuromuscular blockade, whereas II appeared to be the least sensitive (table XII).

DISCUSSION

In this investigation, differences were revealed when the two neuromuscular blocking drugs were studied by measuring the adductor pollicis twitch response to train-of-four nerve stimulation, following the recommended doses.

Atracurium demonstrated a slightly, but not significantly faster onset of action. The time taken for T4 twitch height to recover to 10% of control, reflecting the period of optimal surgical relaxation, was considerably shorter with atracurium. The rate at which T4 twitch height returned towards control values within the period of observation, was also much more rapid with atracurium, clearly illustrating its more rapid and more complete reversal characteristics. However, when using our clinical criteria, the differences were not so marked. Atracurium appeared to be shorter acting than alcuronium because, when used, increments were required more often to maintain surgical relaxation and neostigmine was required less often to antagonize neuromuscular blockade. In all other respects, the two were clinically indistinguishable. Comparable conditions for intubation were observed, and the quality of recovery following administration of neostigmine appeared to be similar.

The effects of halothane on the pharmacodynamics of non-depolarizing neuromuscular blocking drugs are related to its concentraion, but are readily reversible, and have been well documented (Baraka, 1968; Vitez, 1978; Hughes and Payne, 1979; Engbaek, Ørding and Viby-Morgensen, 1983; Stirt et al., 1983); it does not appear to affect the rate of onset of neuromuscular blockade of non-depolarizing blockers. This seems to be related predominantly to the dose of blocking drug (Miller et al., 1972). Few studies have quantified the effects of low concentrations of halothane on the neuromuscular blocking actions of non-depolarizing drugs. However, it has been suggested that the use of 0.5–0.7% halothane is preferable in studies on neuromuscular blockade, since it decreases the variability of individual response. Consequently, fewer patients need to be studied in order to detect differences (Stanski et al., 1979).

Atracurium and alcuronium are both regarded as neuromuscular blockers with medium or intermediate durations of action. Whilst there is no generally agreed definition of medium or intermediate duration of action, definitions based on comparisons of the evoked muscle twitch response using the drug in question with those of suxamethonium and tubocurarine have been proposed (Fahey et al., 1981; Basta et al., 1982). However, quantitative differences may occur in the evoked muscle twitch response to single-twitch, tetanic or train-of-four nerve stimulation (Hughes, 1984). Furthermore, these differences may also arise depending on which of the indices of tetanic or train-of-four muscle twitch response are compared (Lee, Barnes and Katz, 1976). Of the three indices of the train-of-four response we compared, the ratio of the fourth twitch in a train-of-four sequence to that in the train-of-four sequence under control conditions, appeared to give the most sensitive overall index of neuromuscular blockade.

Notwithstanding the use of low-dose halothane, the results of this comparative study of the two neuromuscular blockers would seem to suggest that, when compared with atracurium, alcuronium may not be of medium or intermediate duration. Absolute quantitative support to this observation would require further investigation, perhaps in the absence of halothane. Nonetheless, in clinical practice alcuronium remains a very useful drug for many surgical procedures.

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CROSS-REACTIVITY OF METOCURINE, ATRACURIUM, VECURONIUM AND FAZADINIUM WITH IgE ANTIBODIES FROM PATIENTS UNEXPOSED TO THESE DRUGS BUT ALLERGIC TO OTHER MYONEURAL BLOCKING DRUGS

D. G. HARLE, B. A. BALDO AND M. M. FISHER

SUMMARY

An inhibition assay was used to determine quantitatively the allergenic cross-reactivity of some myoneural blocking drugs not yet released for use in Australia, in the sera of patients who had experienced anaphylactic reactions to neuromuscular blocking drugs. Two of the compounds, metocurine and atracurium were highly cross-reactive with the currently used myoneural blockers; fazadinium was weakly cross-reactive and vecuronium intermediate in potency between these two extremes. From these results, we predict that anaphylactic reactions to these compounds, and particularly to metocurine and atracurium, will occur in some patients allergic to the currently used neuromuscular blocking agents.

Fifty percent of subjects who experience anaphylaxis after the administration of neuromuscular blocking drugs may be sensitive to one or more of these agents. Indeed, some patients show sensitivity to all the available neuromuscular blockers (Vervloet et al., 1979; Fisher and Munro, 1983). As a result, the choice of safe anaesthetic agents for subsequent anaesthesia in such patients may be difficult, particularly if multiple sensitivities are demonstrated by intradermal testing (Fisher, 1979, 1980).

The demonstration of IgE antibodies that bind to alcuronium, tubocurarine, suxamethonium, decamethonium, gallamine and pancuronium (Baldo and Fisher, 1983a, b, c; Harle, Baldo and Fisher, 1984, 1985) in patients who reacted to these drugs provided an opportunity to look for serological cross-reactions to neuromuscular blockers which are not available in Australia and, hence, have not been given to patients here. Cross-reactivity to the drugs metocurine, atracurium, vecuronium and fazadinium was investigated by using the compounds in radioimmunoassay inhibition experiments together with neuromuscular blocker drug-reactive IgE antibodies in sera from sensitive patients. An important consequence of demonstrating binding between a patient's IgE antibodies and the unintroduced drugs is that the same patient may also react adversely to the unencountered myoneural blocker. Therefore, information obtained from this experimental approach promises to be of value to anaesthetists in their efforts to avoid drugs that may provoke adverse reactions in patients with multiple sensitivities to myoneural blocking drugs.

MATERIALS AND METHODS

Subjects and sera

Sera were taken from six patients 1 month after experiencing life threatening (severity grade 3) (Thornton and Lorenz, 1983) anaphylactoid reactions to neuromuscular blocking drugs. Two of these patients (Hu and Qu) were shown by intradermal testing (Fisher, 1981) to have reacted to alcuronium, one patient (Gr) to alcuronium and tubocurarine, one (Pe) to suxamethonium, one

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(Lo) to suxamethonium and pancuronium and one (Mo) to gallamine. One patient (Pe) had a previous severe anaphylactoid reaction to decamethonium on first exposure to a myoneural blocker. Control sera were obtained from 10 members of the hospital staff with no history of adverse reactions to anaesthesia, and cord sera were obtained from the Department of Obstetrics, Royal North Shore Hospital.

Drugs

Choline chloride was obtained from Sigma Chemical Co., St Louis, Mo, U.S.A.; tubocurarine chloride (batch No. B 56572), decamethonium bromide (lot 9L2262) and suxamethonium chloride (batch A.N. 2917) from Wellcome Australia, Roseberry, N.S.W., Australia; alcuronium dichloride (batch No. B 1823) from Hoffmann-La Roche, Basle, Switzerland; gallamine triethiodide (batch No. 10105) from May and Baker, Victoria, Australia; pancuronium bromide (batch No. 2136751) and vecuronium bromide from Organon Oss, Holland; fazadinium bromide (batch No. MM 069923) from Glaxo Laboratories, Victoria, Australia; metocurine iodide (batch No. 6FH43A) from Eli Lilly and Company, Indianapolis, U.S.A.; atracurium besylate (lot 385A) from Wellcome Foundation, London, U.K. Triethylcholine iodide was synthesized (Harle, Baldo and Fisher, 1985) from 2-diethylaminoethanol using the method of Dauterman and Mehrotra (1963).

Preparation of drug–solid phase complexes

Alcuronium, tubocurarine, suxamethonium/decamethonium and gallamine. Preparation of drug–solid phase complexes for alcuronium (Baldo and Fisher, 1983b), tubocurarine (Baldo and Fisher 1983c), suxamethonium/decamethonium (Harle, Baldo and Fisher, 1984) and gallamine (Harle, Baldo and Fisher, 1985) has been previously reported.

Vecuronium. Vecuronium bromide 60 mg in 6 ml of distilled water was covalently coupled to 500 mg of Epoxy-activated Sepharose 6B (Pharmacia) by adjusting the pH to 12.4 with sodium hydroxide 2.5 mol litre^{-1} and gently shaking with the activated Sepharose at 25 °C for 20 h. After washing with water, borate buffer 0.1 mol litre^{-1}, pH 8, and acetate buffer 0.1 mol litre^{-1}, pH 4, remaining free activated groups were blocked by incubation with ethanolamine 1 mol litre^{-1}, pH 9, at room temperature for 4 h.

Direct binding and inhibition assays

Direct binding and inhibition radioimmunoassay studies were carried out as previously described (Baldo and Fisher, 1983b). Briefly, for inhibition studies serum 50 µl, appropriately diluted, was incubated for 1 h with 50 µl of a

TABLE I. *Cross-reactivity of metocurine, atracurium, vecuronium and fazadinium. Inhibition studies with sera containing IgE antibodies to alcuronium, tubocurarine, pancuronium, suxamethonium, decamethonium or gallamine.* [a] *Used at the following dilutions: Hu (choline–Sepharose), Pe (choline–Sepharose, tubocurarine–Sepharose), 1:12; Gr (tubocurarine–Sepharose, alcuronium–Sepharose), Pe (alcuronium–Sepharose), 1:8; Lo (tubocurarine–Sepharose), 1:4; Gr (vecuronium–Sepharose), Hu (triethylcholine–Sepharose), Lo (choline–Sepharose, triethylcholine–Sepharose), Mo (vecuronium–Sepharose), Pe (triethylcholine–Sepharose), 1:2; Qu (alcuronium–Sepharose), undiluted.* [b] *Amount needed to produce 50% inhibition of the uptake of* ^{125}*I-anti-human IgE.* [c] *Amounts shown are for 30% inhibition. Fifty percent inhibition not achieved*

		Drug–solid phase complex: Sepharose	Amount (nmol) of blocker needed for significant inhibition[b]			
Serum[a]	Drug reacted to	linked to	Metocurine	Atracurium	Vecuronium	Fazadinium
Gr	Alcuronium/ tubocurarine	Vecuronium	0.5	0.38	0.2	0.55
		Tubocurarine	9.0	4.6	24	42
		Alcuronium	2.1	1.7	22	19
Hu	Alcuronium	Choline	1.1	32	6.8	1.0
		Triethylcholine	3.7	66	10	15
Lo	Suxamethonium/ pancuronium	Choline	< 0.1	0.4	1.4	21
		Triethylcholine	1.6	4.6	0.6	11
		Tubocurarine	19[c]	7.4[c]	170[c]	160[c]
Mo	Gallamine	Vecuronium	2.0[c]	22[c]	0.5[c]	2.0[c]
Pe	Suxamethonium/ decamethonium	Choline	< 0.1	< 0.1	1.7	14
		Triethylcholine	0.3	3.2	2.4	20
		Tubocurarine	1.3	1.2	190	280
		Alcuronium	4.0	5.7	52	1000
Qu	Alcuronium	Alcuronium	23[c]	21[c]	30[c]	100[c]

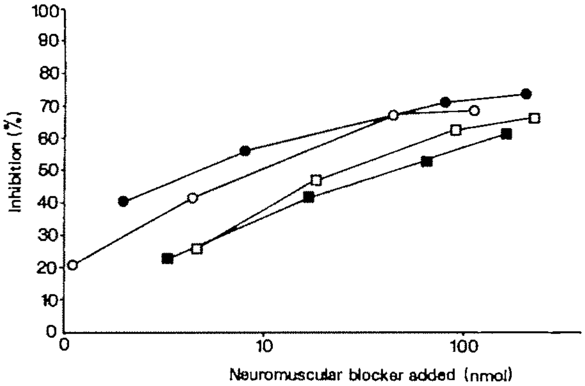

FIG. 1. Inhibition by the myoneural blockers metocurine (○), atracurium (●), vecuronium (□) and fazadinium (■) of IgE binding in serum Gr to tubocurarine–Sepharose complex. Serum Gr was used at a dilution of 1:8.

solution of the drug being tested before the addition of the drug–solid phase complex (6 mg in 100 μl) and then ^{125}I-labelled anti-human IgE. After washing, the amount of label retained by the solid phase was estimated by counting in a gamma spectrometer.

RESULTS

Table I summarizes results obtained from inhibition studies in which patients' sera were preincubated with each of the four myoneural blockers (metocurine, atracurium, vecuronium and fazadinium), using five different drug–solid supports (alcuronium–, tubocurarine–, vecuronium–, choline–, and triethylcholine–Sepharose). Figure 1 shows inhibition results obtained for one of the sera, serum Gr with tubocurarine–Sepharose as drug support. All of the drugs inhibited, although considerable variation was evident in their potencies.

Metocurine and atracurium were generally more potent inhibitors than vecuronium and fazadinium and showed little variation between supports and sera. For example, values for metocurine ranged from 50 % inhibition with less than 0.1 nmol of drug for sera Pe and Lo with choline–Sepharose up to only 30 % inhibition with 23 nmol of drug for serum Qu with alcuronium–Sepharose. Atracurium varied from less than 0.1 nmol of drug for serum Pe with choline–Sepharose for 50 % inhibition up to 22 nmol of drug with serum Mo with vecuronium-Sepharose for 30 % inhibition.

On the other hand, relatively weak inhibition was observed for fazadinium with most sera and considerable variation in potency was observed. In particular, for serum Pe with alcuronium–Sepharose, 1000 nmol of drug was required for 50 % inhibition, whereas as little as 0.55 nmol of drug was needed with serum Gr with vecuronium–Sepharose.

Vecuronium was generally intermediate as an inhibitor but was clearly the most potent inhibitor with vecuronium–Sepharose, requiring only 0.2 nmol of drug with serum Gr to provide 50 % inhibition. In contrast, 170 nmol of drug was required for serum Lo with tubocurarine–Sepharose for 30 % inhibition.

From table I, it is clear that pronounced variation in the potencies of the relaxant drugs occurred between the solid supports for the same serum. For example, serum Pe with choline–Sepharose required less than 0.1 nmol of metocurine to give 50 % inhibition, whereas 1000 nmol of fazadinium was needed for the same amount of inhibition with alcuronium–Sepharose. With serum Lo, less than 0.1 nmol of metocurine was needed for 50 % inhibition with choline–Sepharose, while 170 nmol of vecuronium was required for only 30 % inhibition with tubocurarine–Sepharose.

Normal and cord sera all gave low radioactive uptakes with each of the five drug–solid supports in direct binding radioimmunoassays as reported previously (Baldo and Fisher, 1983a, b, c; Harle, Baldo and Fisher, 1984, 1985).

DISCUSSION

We have previously demonstrated IgE antibodies that bind to neuromuscular blockers in sera from drug-sensitive patients and identified tertiary and quaternary ammonium ions as the allergenic determinants on the drug molecules (Baldo and Fisher 1983a, b, c; Harle, Baldo and Fisher, 1984, 1985). From our studies, it has become evident that many of these patients have multiple sensitivities to such relaxants. In order to determine whether such patients are sensitive to myoneural blockers not yet available for use in Australia, we performed inhibition studies with metocurine, atracurium, vecuronium and fazadinium.

Our results showed that cross-reactivity does exist between drug-reactive IgE antibodies and the four relaxants. With all six sera examined, varying degrees of inhibition were observed. Metocurine and atracurium were the strongest inhibitors, while fazadinium was invariably the least potent. Vecuronium was moderate in potency as an inhibitor, but was clearly the most potent with the drug-support vecuronium–Sepharose, as might be expected.

Patient Qu proved interesting in that direct binding assay studies with the five drug-supports (not shown) resulted in a positive uptake for alcuronium–Sepharose only. In the inhibition studies, however, all four relaxants showed moderate inhibition.

From these studies, it is clear that sensitive patients unexposed to such drugs as metocurine, atracurium, vecuronium and fazadinium, which are not currently administered in anaesthesia in Australia, have drug-reactive IgE antibodies in their sera that are capable of cross-reacting with these relaxants. As a consequence, subsequent exposure to these drugs may well result in an adverse reaction. Bronchospasm has recently been reported in England in a patient given atracurium. A positive skin test was obtained to the neuromuscular blocker but not to other drugs used during the operation or to other relaxants, suggesting that the patient was specifically hypersensitive to atracurium (Sale, 1983). Anaphylactic reactions to fazadinium have also been reported (Alexander, 1979) and the drug was found to produce massive histamine release at low concentrations from leucocytes in a patient who experienced an anaphylactic reaction to suxamethonium (Assem, Frost and Levis, 1981).

Although the four drugs studied all contain at least one quaternary ammonium group, our previous findings suggest that compounds containing tertiary ammonium ions are also capable of cross-reacting, perhaps less strongly, with drug-reactive IgE antibodies. It should be noted that vecuronium, unlike the other three drugs and most other myoneural blockers in current use, contains one quaternary ammonium and one tertiary ammonium ion. As a result, the likelihood of cross-linking of two IgE molecules on a mast cell resulting in the release of histamine (Baldo and Fisher, 1983b) may be reduced. Of course, proof that such drug-mediated cross-linking occurs has yet to be provided.

In conclusion, results presented here and our previous findings (Baldo and Fisher 1983a, b, c; Harle, Baldo and Fisher, 1984, 1985) demonstrate that, once a patient has been sensitized to a particular neuromuscular blocking drug, there is a strong possibility of cross-reactivity with other myoneural blockers that contain quaternary or tertiary ammonium ions. Failure to appreciate such cross-sensitivity has led to second severe reactions to such drugs in the past (Fisher, 1981) and, as the majority of severe anaphylactic reactions to these drugs occur on first exposure (Fisher and Munro, 1983), the use of a "new relaxant" in a patient who has reacted to neuromuscular blocking drugs previously may not decrease the hazard of a subsequent reaction.

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MEPTAZINOL—A CAUSE OF RESPIRATORY DEPRESSION IN GENERAL ANAESTHESIA

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SUMMARY

The respiratory effects of meptazinol 1 mg kg^{-1} have been compared with those of pethidine 0.5 mg kg^{-1} and 1 mg kg^{-1} in a double-blind trial in 30 patients undergoing arthroscopic meniscectomy under general anaesthesia. Respiratory depression was seen in all treatment groups. Pethidine 1 mg kg^{-1} produced respiratory depression which was greater than that produced by meptazinol 1 mg kg^{-1}. The least depressant respiratory effects were seen in the group receiving pethidine 0.5 mg kg^{-1}. We submit that the measurement of tidal volume enhances the assessment of the respiratory effects of analgesic drugs during anaesthesia.

Meptazinol (m-(3-ethyl-1-methyl hexahydro-1-H-azepin-3-yl) phenol hydrochloride is a synthetic analgesic drug with opioid agonist/antagonist properties which belongs to the hexahydroazepine group of drugs. It has been shown to have potent analgesic properties in animals (Goode and White, 1971) and yet does not appear to interact with those receptors mediating respiratory depression, as either an agonist or an antagonist, in the rat (Spiegel and Pasternak, 1984).

In man, it has been used successfully to relieve postoperative pain (Paymaster, 1976, 1977; Moyes, Miller and Aldridge, 1979; Hedges and Turner, 1983), the analgesic effect being associated with only moderate sedation and minimal respiratory depression when used either following surgery (Paymaster, 1977) or in awake volunteers (Jordan et al., 1979). Cohen and colleagues (1983) reported that the drug produced less respiratory depression then morphine, but cast doubt on its efficacy as an analgesic.

The property of potent analgesia, which is associated with minimal respiratory depression, would make meptazinol very useful during surgical procedures. There are, however, few reported studies on its use during anaesthesia.

Verschraegan and co-workers (1976), following an open study on ventilated patients, did not recommend the use of meptazinol during operation, primarily because of the high incidence of postoperative nausea and vomiting, features also observed by other workers (Oosterlinck and De Sy, 1975; Gibbs and Johnson, 1980; Slattery et al., 1981).

Slattery and colleagues (1982) investigated the use of meptazinol during surgery in an open study on spontaneously breathing anaesthetized patients. They used fixed doses which were unrelated to body weight, and compared the effects with those obtained in a control group who received no analgesia. These workers measured changes in respiratory frequency and end-tidal carbon dioxide concentration and concluded that meptazinol caused respiratory depression. Neither tidal volume nor minute volume were measured.

In a further open study involving spontaneously breathing anaesthetized patients, Slattery and colleagues (1983) investigated the respiratory effects of up to 100 mg of meptazinol i.v. and compared these with the effects of up to 40 mg of pethidine and concluded that meptazinol offered no advantage over pethidine. In both groups there was a statistically significant decrease in respiratory rate, but not in tidal volume. The volumes were measured with an electronic Wright's respirometer which was incorporated into a non-standard

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anaesthetic circuit. The inaccuracies of these inferential anemometers are well known (Nunn and Ezi-Ashi, 1962).

The apparent discrepancy in both the respiratory depressant and the analgesic effects of meptazinol in animals, postoperative patients and awake volunteers compared with those under anaesthesia warranted further investigation. This study was performed to determine the respiratory effects of i.v. meptazinol during anaesthesia in spontaneously breathing anaesthetized patients.

PATIENTS AND METHODS

Patients

Thirty patients undergoing elective surgery for arthroscopic menisceсtomy were investigated in a double-blind study, which had been approved by the local ethics committee. All patients were seen before operation to assess their fitness and to obtain informed consent. Only those of ASA Grade 1 were admitted to the trial.

The patients were randomly allocated to three groups of 10. The first group received pethidine 0.5 mg kg^{-1}, the second pethidine 1 mg kg^{-1} and the third group meptazinol 1 mg kg^{-1}. There has been debate as to the equi-analgesic dosage of these drugs. The manufacturers claim that the ratio of meptazinol to pethidine is 1:1, based on volunteer studies, while Slattery and colleagues (1981) suggested a ratio of 2.4:1 from their study on postoperative analgesic consumption. We, therefore, chose the two doses of pethidine which corresponded with these values with which to compare meptazinol. It was felt that, if Slattery and colleagues were correct in their assessment, a dose of meptazinol 0.5 mg kg^{-1} might not provide adequate analgesia and would be ethically unacceptable.

The analgesic was diluted to 30 ml with water for injection and administered over 3 min using a Sage syringe pump, model 355. This technique of analgesic infusion was determined as a result of an open study which showed that a more rapid infusion, or a bolus injection caused immediate apnoea in some patients. An anaesthetist not involved in the study prepared the analgesic drug for infusion, thereby allowing the investigators, who would subsequently calculate the results from the records obtained, and recovery nurse making the postoperative assessment to remain "blind" to the drug used.

Anaesthesia

Patients were pre-medicated with diazepam 0.15 mg kg^{-1} orally 2 h before the operation. Anaesthesia was induced with methohexitone 1–1.5 mg kg^{-1} preceded by atropine 0.6 mg i.v. and metoclopramide 10 mg i.v. Suxamethonium 1 mg kg^{-1} was given, the larynx sprayed with 10% lignocaine and a cuffed oral tracheal tube passed. The lungs were ventilated manually until spontaneous respiration resumed. A mixture of 30% oxygen in nitrous oxide, with 1% halothane added, at a fresh gas flow of 100 ml kg^{-1} min^{-1} from a Mapleson A system was used throughout the procedure. The same, recently serviced, Fluotec Mark 2 vaporizer was used for all patients in the study.

Measurements

After the return of spontaneous respiration, recordings of tidal volume and tidal carbon dioxide concentration against time were commenced and continued for the duration of the surgical procedure. Within about 10 min, a steady state of spontaneous respiration under anaesthesia was achieved. This was defined as a steady respiratory frequency and tidal volume, and a stable end-tidal carbon dioxide concentration.

Tidal volume was obtained from the output of a wet wedge spirometer (O'Connor et al., 1985) using the bag-in-bottle principle (Nunn, 1956). Carbon dioxide concentration was recorded continuously using an Instrumentation Laboratories IL200 capnograph, which sampled gas at 200 ml min^{-1} from the proximal end of the tracheal tube. Once a 3-min record of the above variables had been obtained during the steady state of respiration and before any surgical stimulation, an i.v. infusion of the allocated drug was given.

For a 5-min period following the start of this infusion, no surgical stimulation was permitted. There then followed a series of preliminary surgical stimuli of increasing severity which included in some cases the application of an esmarch bandage, and in all cases application of a limb tourniquet and commencement of the operation with the insertion of the arthroscope. At the end of the operation, when all instruments were removed from the knee joint before suturing the skin, the halothane was switched off and the recordings of volume and end-tidal carbon dioxide concentration continued for a further 1 min. After the knee was bandaged, the trachea was extubated

TABLE I. *Details of patients studied*

	Pethidine 0.5 mg kg^{-1}	Pethidine 1.0 mg kg^{-1}	Meptazinol 1.0 mg kg^{-1}
No. patients	10	10	10
M/F	7/3	8/2	8/2
Age (yr)			
Mean (SD)	31.9 (11.6)	30.3 (11.9)	32.8 (9.1)
Weight (kg)			
Mean (SD)	73.3 (11.0)	76.3 (12.0)	70.4 (12.2)

and the patient transferred to the recovery room where oxygen 4 litre min^{-1} was administered via an MC mask. The recovery nurse recorded the time at which the patient was able to obey a simple command and also evaluated the general condition of the patient 20 min later.

Calculations were made from the continuous record of tidal volume to give minute volume, by summation of each tidal expiration in the chosen period. Respiratory frequency was derived from the same record. End-tidal carbon dioxide concentration was calculated from the continuous record of carbon dioxide concentration against time. The measurements were made at the steady state of respiration, at 1, 2, 3 and 4 min after the start of the infusion of analgesic, at each of the preliminary surgical stimuli mentioned above and, finally, once the halothane was discontinued at the end of the operative procedure.

In the post-operative period the patients were given an opiate analgesic if they were in pain, and the time of the administration was noted. Every patient was seen on the following day by one of the investigators and any side effects of the drug recorded.

RESULTS

Table I shows the number of patients in each treatment group, together with the mean ages and

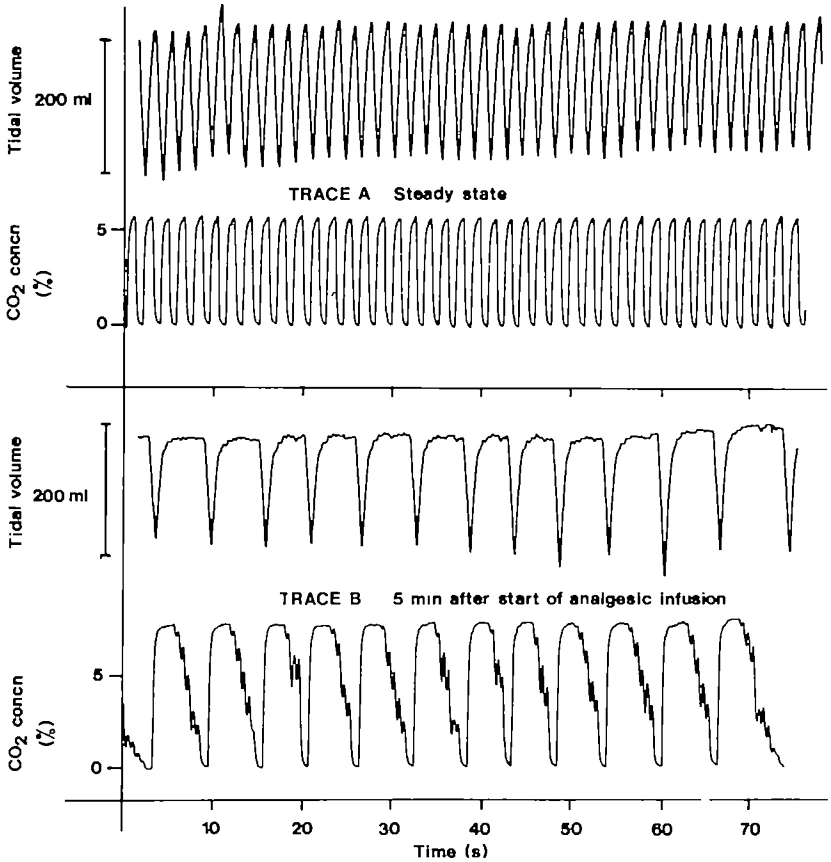

FIG. 1. Tracing of tidal volume and carbon dioxide concentration against time in a spontaneously breathing anaesthetized patient. Trace A = steady state of respiration under anaesthesia. Trace B = 5 min after the start of an infusion, over 3 min, of pethidine 1 mg kg^{-1}.

TABLE II. *Respiratory frequency (b.p.m.) during steady state of respiration, 1, 2, 3 and 4 min after the start of the analgesic infusion and at the times of various pre-surgical and surgical stimuli. (Mean values, SEM and range). Esm. = esmarch bandage; Tour. = tourniquet; Scope = arthroscope; Hal. off = halothane off*

	Steady state	Time after start of infusion (min)							
		1	2	3	4	Esm.	Tour.	Scope	Hal. off
Pethidine 0.5 mg kg^{-1}									
Mean	25.3	28.1	23.8	19.3	18.0	17.6	18.9	21.1	27.9
SEM	0.8	2.2	1.7	1.9	2.2	2.1	1.7	1.6	2.1
Range	21.0–31.0	20.0–50.0	12.0–35.0	3.0–31.0	0.0–30.0	8.0–24.0	7.0–27.0	12.0–30.0	16.0–42.0
Pethidine 1.0 mg kg^{-1}									
Mean	29.7	27.3	19.9	11.9	6.7	5.0	7.5	12.9	22.4
SEM	2.5	3.0	3.2	3.8	3.0	2.2	1.9	2.0	2.8
Range	20.0–38.0	16.0–39.0	9.0–33.0	0.0–28.0	0.0–22.0	0.0–10.0	0.0–12.0	7.0–21.0	11.0–34.0
Meptazinol 1.0 mg kg^{-1}									
Mean	23.2	19.3	13.3	10.5	12.4	10.4	12.6	13.9	23.2
SEM	1.7	2.2	2.5	2.2	2.0	1.7	2.0	2.2	3.0
Range	16.0–35.0	7.0–32.0	0.0–25.0	0.0–21.0	1.0–21.0	6.0–16.0	4.0–24.0	5.0–28.0	13.0–45.0

TABLE III. *Minute volume (litre min^{-1}) during steady state of respiration, 1, 2, 3 and 4 min after the start of the analgesic infusion and at the times of various pre-surgical and surgical stimuli. (Mean values, SEM and range). Esm. = esmarch bandage; Tour. = tourniquet; Scope. = arthroscope; Hal. off = halothane off*

	Steady state	Time after start of infusion (min)							
		1	2	3	4	Esm.	Tour.	Scope	Hal. off
Pethidine 0.5 mg kg^{-1}									
Mean	6.3	5.6	4.7	3.7	3.3	3.8	4.8	5.6	6.6
SEM	0.4	0.5	0.5	0.4	0.5	0.3	0.4	0.5	0.4
Range	4.3–9.1	3.1–10.3	2.6–8.7	0.7–6.5	0.0–6.1	2.1–5.2	2.6–7.9	3.7–9.2	4.4–9.4
Pethidine 1.0 mg kg^{-1}									
Mean	6.1	4.6	2.6	1.3	0.8	1.7	2.5	3.6	5.1
SEM	0.3	0.4	0.6	0.4	0.4	0.6	0.6	0.2	0.6
Range	5.1–7.3	3.0–5.6	0.3–4.8	0.0–3.0	0.0–2.5	0.0–2.6	0.0–4.2	3.0–4.4	3.6–8.6
Meptazinol 1.0 mg kg^{-1}									
Mean	5.4	3.2	2.0	1.8	2.5	3.4	3.4	4.1	5.7
SEM	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.5	0.6
Range	4.5–8.5	0.5–4.9	0.0–3.6	0.0–4.0	0.6–3.7	2.4–4.2	2.1–5.1	2.0–6.3	3.8–9.1

weights, and respective standard deviations.

Figure 1 shows part of the continuous recording of tidal volume and carbon dioxide concentration against time for one patient. This patient was a 60-kg, 22-year-old female patient who received pethidine 60 mg. Trace A was taken during steady state anaesthesia and trace B 5 min after the start of the infusion of the analgesic.

Tables II, III and IV show the mean, standard error of the mean and the range for frequency, minute volume and end-tidal carbon dioxide concentration at the specific times mentioned above.

The median values for each variable, minute volume, respiratory frequency and end-tidal carbon dioxide concentration, were calculated for each drug treatment group, at the above times and are shown in figure 2. This figure shows that the

TABLE IV. *End-tidal carbon dioxide concentration (%) during steady state of respiration, 1, 2, 3 and 4 min after the start of the analgesic infusion and at times of various pre-surgical and surgical stimuli. (Mean values, SEM and range). Esm. = esmarch bandage; Tour. = tourniquet; Scope = arthroscope; Hal. off = halothane off*

	Steady state	Time after start of infusion (min) 1	2	3	4	Esm.	Tour.	Scope	Hal. off
Pethidine 0.5 mg kg^{-1}									
Mean	6.5	6.5	6.8	7.1	7.4	7.5	7.7	7.4	6.9
SEM	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.3	0.2
Range	5.8–7.2	5.6–7.6	5.4–8.2	6.4–8.6	6.3–8.6	6.8–8.5	7.0–9.2	6.4–9.6	5.8–8.8
Pethidine 1.0 mg kg^{-1}									
Mean	6.4	6.8	6.8	7.3	8.2	8.4	8.1	8.6	7.5
SEM	0.3	0.3	0.4	0.4	0.5	0.4	0.4	0.5	0.3
Range	4.9–7.4	5.9–7.8	5.2–8.0	5.9–8.6	7.4–9.6	7.5–8.8	7.0–8.8	7.0–10.4	6.6–8.4
Meptazinol 1.0 mg kg^{-1}									
Mean	6.2	6.2	6.6	7.2	7.4	6.8	7.3	7.3	6.7
SEM	0.2	0.2	0.3	0.3	0.3	0.4	0.3	0.3	0.3
Range	5.2–7.4	5.3–7.4	5.4–7.8	5.7–8.4	6.0–8.6	5.8–7.6	6.0–8.8	6.0–8.9	5.2–8.9

minute volume and the respiratory frequency were decreased in all three treatment groups after the infusion, and that the end-tidal carbon dioxide concentration had increased. These changes were indicative of respiratory depression of varying degree. The most severe occurred in the group receiving pethidine 1 mg kg^{-1} and the least in the group which received pethidine 0.5 mg kg^{-1}.

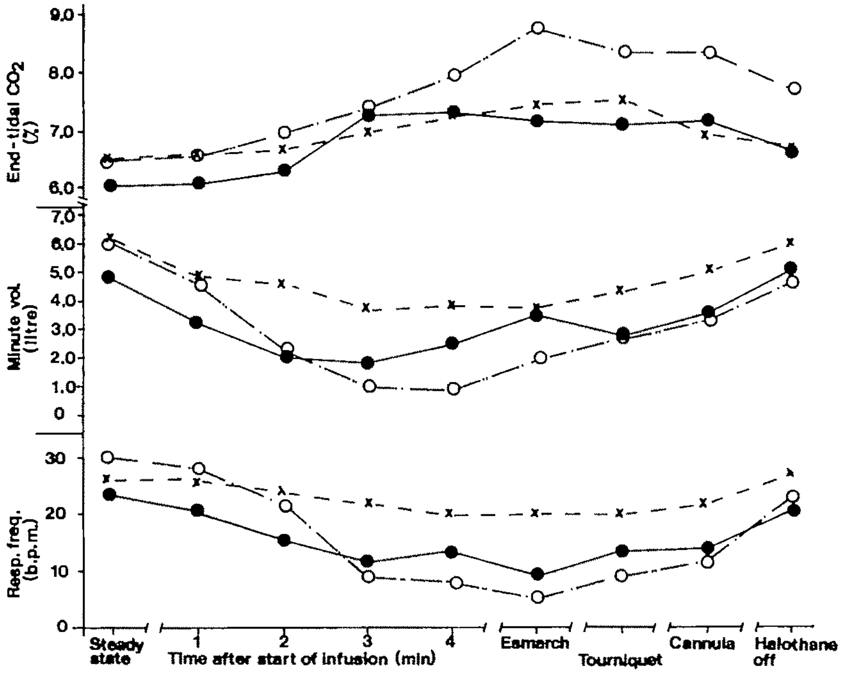

FIG. 2. Median values of frequency, minute volume, and end-tidal carbon dioxide concentration for each treatment group during steady state of respiration under anaesthesia, 1, 2, 3 and 4 min after the start of the analgesic infusion, at times of various surgical stimulation and at the time at which the halothane was discontinued. x = Pethidine 0.5 mg kg^{-1}; ○ = pethidine 1.0 mg kg^{-1}; ● = meptazinol 1.0 mg kg^{-1}.

Statistical analysis

Kruskal–Wallis one way analysis of variance (Siegel, 1956) showed that the three treatment groups were homogeneous. There were no statistically significant differences in the duration of the operation, the duration of the anaesthetic, the age, sex or weight of the patients between the three treatment groups. Additionally, the same analysis showed that there were no significant differences between the steady state values of any of the variables calculated for the three treatment groups.

A Wilcoxon paired signed rank test (Siegel, 1956) was used to compare, for each individual treatment group, the raw data from the steady state of respiration with those before surgical stimulation but after infusion of the analgesic drug. Table V shows the levels of statistical significance. The measurements of the respiratory variables were made once a steady state of anaesthesia was achieved, as previously described. We believe, therefore, that these results illustrate the statistical significance of the respiratory depression which is attributable, in the main, to the analgesic drug given, because any changes as a result of the anaesthetic sequence were minimal.

Statistical analyses, using the Mann–Whitney *U* test (Siegel, 1956) were also performed to compare treatment groups. For these analyses the raw data used for the comparison were the differences between the steady-state values and those at the subsequent time. Table VI shows the levels of statistical significance between groups at the measurement times following the various analgesic infusions.

TABLE V. *Levels of statistical significance, from the Wilcoxon paired signed rank test, comparing the results from the steady state of respiration with those following analgesic infusion but before surgical stimulation was permitted.* (−) *Indicates that the values following analgesic infusion were lower than those during the steady state of respiration;* (+) *indicates that the values following analgesic infusion were higher than those during the steady state of respiration*

	Frequency	Minute volume	End-tidal carbon dioxide concn
Pethidine 0.5 mg kg^{-1}	0.001 (−)	0.00001 (−)	0.001 (+)
Pethidine 1.0 mg kg^{-1}	0.00001 (−)	0.00001 (−)	0.001 (+)
Meptazinol 1.0 mg kg^{-1}	0.00001 (−)	0.00001 (−)	0.001 (+)

As may be seen from figure 2, respiratory depression decreased as the operative procedure continued. By the end of the operation, there was no difference between the steady-state and the "halothane off" measurements, except in the group receiving pethidine 1 mg kg^{-1}. In this group, there was a statistically significant difference between measurements taken when halothane was switched off compared with the results at steady-state for both respiratory frequency ($P < 0.02$) and end-tidal carbon dioxide concentration ($P < 0.05$), indicating that respiration was still depressed.

There was no statistically significant difference, shown by the Kruskal–Wallis one-way analysis of variance, between the three treatment groups in the condition of the patient in the recovery room, or in the requirement for postoperative opiate analgesia.

We investigated whether the percentage changes in minute volume, with respect to steady state, were solely dependent upon the percentage changes in frequency with respect to steady state. We performed linear regression analyses to consider these percentage changes and the equations for each treatment group alone are shown in table VII. We also performed Student's *t* tests and found that the intercepts were statistically significantly different from zero. The coefficients of correlation, *r*, and the *P* values thus obtained are shown in table VII.

DISCUSSION

Reports on the intraoperative use of meptazinol are infrequent. This, the first double-blind, weight-related study, has shown, as previously suggested (Slattery et al., 1982), that meptazinol causes respiratory depression and that this respiratory depression is less than that found with pethidine 1 mg kg^{-1} but greater than that found with pethidine 0.5 mg kg^{-1}. These two doses of pethidine reflect the debate regarding the analgesic potency of meptazinol. The design of this study does not allow us to comment on the relative potency or duration of action of meptazinol compared with pethidine. We can, however, state that the intraoperative conditions were satisfactory in all patients and we were unable to demonstrate any difference in analgesic requirements in the postoperative period.

It may be that meptazinol is less potent than pethidine. Assuming that meptazinol and pethidine are equipotent in a 1 mg to 1 mg dosage, our study

TABLE VI. *Levels of statistical significance, from the Mann Whitney* U *test, comparing treatment groups at times following the start of the analgesic infusion, at the time of surgical stimulation and when the halothane was switched off. Where a* P *value is shown (e.g. for a comparison of pethidine 0.5 mg* kg^{-1} v. *meptazinol* 1.0 *mg* kg^{-1}) *this indicates that there is a greater, statistically significant, degree of respiratory depression in the group treated with meptazinol. Freq. = Frequency; MV = minute volume;* CO_2 *= end-tidal carbon dioxide concentration*

Time	Variable	Pethidine 0.5 mg kg^{-1} *v.* meptazinol 1.0 mg kg^{-1}	Meptazinol 1.0 mg kg^{-1} *v.* pethidine 1.0 mg kg^{-1}	Pethidine 0.5 mg kg^{-1} *v.* pethidine 1.0 mg kg^{-1}
1 min after the start of infusion	Freq.	0.01	ns	0.02
	MV	0.01	ns	ns
	CO_2	ns	ns	ns
2 min after the start of infusion	Freq.	0.01	ns	0.002
	MV	0.05	ns	0.02
	CO_2	ns	ns	ns
3 min after the start of infusion	Freq.	0.01	ns	0.002
	MV	ns	ns	0.02
	CO_2	ns	ns	ns
4 min after the start of infusion	Freq.	ns	0.002	0.002
	MV	ns	0.001	0.02
	CO_2	ns	0.025	0.05
Esmarch	Freq.	ns	0.01	0.01
	MV	ns	0.01	0.025
	CO_2	ns	ns	ns
Tourniquet	Freq.	0.05	0.002	0.002
	MV	ns	0.02	0.02
	CO_2	ns	0.02	ns
Arthroscope	Freq.	0.05	0.02	0.002
	MV	ns	0.05	0.02
	CO_2	ns	0.05	0.02
Halothane off	Freq.	ns	0.02	0.02
	MV	ns	ns	0.05
	CO_2	ns	ns	ns

shows that there would be advantages in using meptazinol as an analgesic in anaesthetized patients breathing spontaneously. If, however, the work of Slattery and co-workers (1981) is correct and an equipotent dosage is in the ratio of 2.4 mg of meptazinol to 1 mg of pethidine, then there would be no advantage in using meptazinol in these circumstances. Further work on the intra-operative potency of meptazinol is required.

TABLE VII. *Linear regression equations for the results of the percentage changes in frequency and minute volume following infusion of the analgesic drug compared with steady state of respiration. The* P *value indicates the statistical significance of the intercept from zero, by using Student's* t *test, and* r *is the coefficient of correlation*

	Equation	*r*	*P*
Pethidine 0.5 mg kg^{-1}	$MV\% = -18.3 + 0.88\,Freq\%$	0.84	0.001
Pethidine 1.0 mg kg^{-1}	$MV\% = -24.1 + 0.82\,Freq\%$	0.94	0.001
Meptazinol 1.0 mg kg^{-1}	$MV\% = -30.2 + 0.62\,Freq\%$	0.86	0.001

Our measurements, obtained continuously using standard anaesthetic circuitry showed, contrary to the work of Slattery and colleagues (1982, 1983), that there are profound changes in both minute volume and frequency following the administration of either pethidine or meptazinol. The linear regression analyses performed on the percentage changes in minute volume and frequency following analgesic infusion compared with steady state showed that the decrease in minute volume was not solely dependent upon a decrease in respiratory frequency.

In addition, our studies have shown that end-tidal carbon dioxide concentration is a slowly responding measure of respiratory status when compared with either volume or frequency. Changes in end-tidal carbon dioxide concentration may reflect changes in either the metabolic state or the ventilation/perfusion ratios of the lungs and the effects of pethidine and meptazinol on these variables have not been fully evaluated. We postulate that, for reliable analyses of respiratory effects of analgesic drugs, minute volume, respiratory frequency and end-tidal carbon dioxide concentration should all be measured.

In our patients the onset of respiratory depression induced by meptazinol was rapid, being both clinically and statistically significant 1 min after the start of the infusion of the analgesic, as indicated by respiratory frequency ($P < 0.01$) and minute volume ($P < 0.01$). The respiratory depression which we observed was mitigated partially by the surgical stimulation of the operative procedure and presumably also by the pharmacokinetic profile of the analgesic drug.

All the patients in this study were ASA grade 1. Respiratory depression to the degree experienced in this study may well have serious clinical implications in poorer risk patients. None of the patients in our study received opiate premedication. The use of meptazinol with this type of premedication may well result in even more marked respiratory depression.

All three treatments produced satisfactory analgesia and postoperative analgesic requirements were minimal. Many previous studies with meptazinol have highlighted the high incidence of nausea and vomiting associated with this drug, but this was not our experience. We attribute this difference to the routine administration of metoclopramide before the induction of anaesthesia.

In conclusion, we believe that meptazinol, when used in this anaesthetic sequence, produces both clinically and statistically significant respiratory depression.

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IN VITRO DEGRADATION OF ATRACURIUM IN HUMAN PLASMA

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SUMMARY

The degradation of atracurium and the formation of laudanosine was examined in vitro *in both Sorensen buffer and human plasma using sensitive, specific high pressure liquid chromatographic assays to determine drug concentrations. At normal physiological pH and temperature, the degradation of atracurium was threefold more rapid in plasma than in buffer. Laudanosine is the major end-product of atracurium degradation in buffer or in plasma; its production is more rapid in plasma than in buffer. Dilution of plasma constituents or the use of diisopropylfluorophosphate (a potent esterase inhibitor), slows the degradation of atracurium and the production of laudanosine. We conclude that, although ester hydrolysis is the major metabolic pathway of atracurium degradation, Hofmann elimination provides a "safety net" in its clinical use.*

Atracurium degrades spontaneously via Hofmann elimination and is metabolized by non-specific esterases (dual pathways (Hughes and Chapple, 1981)). Although it has been suggested that Hofmann elimination contributes substantially to the total elimination of atracurium, we and others have noted that the degradation of atracurium was several times faster in plasma than in buffer (at the same pH and temperature) (Merrett, Thompson and Webb, 1983; Stiller, Brandom and Cook, 1984). These data suggest that ester hydrolysis is a more important factor in the degradation of atracurium than Hofmann elimination. We were interested, therefore, in determining the relative role of each pathway in the *in vitro* degradation of atracurium in buffer and in human plasma.

MATERIALS AND METHODS

Atracurium 24 nmol (28800 ng) was added to 10 ml of Sorensen buffer (pH 7.3), to 10 ml of fresh pooled human plasma (pH adjusted to 7.3), or to 1:1 dilutions of buffer and plasma (pH 7.3). In addition, diisopropylfluorophosphate (DIFP) (30 µmol), an esterase inhibitor, was incubated with 10 ml of buffer or plasma for 30 min; atracurium was then added. The solutions were mixed thoroughly with atracurium and incubated at 37 °C. At timed intervals (0, 20, 40, 60, 120 and 180 min), 0.4-ml aliquots were withdrawn, acidified with 3N HCl 0.01 ml and frozen to −70 °C in a mixture of dry ice and acetone. Atracurium and laudanosine were determined at each time by sensitive, specific high pressure liquid chromatography using assays developed in our laboratory (Stiller, Brandom and Cook, 1984). These assays are second generation modifications of the original atracurium assay described by Neill and Jones (1983).

The monoquaternary alcohol metabolite of atracurium (30000 ng) was added to 10 ml of Sorensen buffer (pH 7.3) or to 10 ml of fresh pooled human plasma (pH adjusted to 7.3). In addition, DIFP was incubated with 10 ml of plasma or buffer for 30 min; the monoquaternary alcohol was then added. The solutions were mixed thoroughly with the monoquaternary alcohol and incubated at 37 °C. At timed intervals (see above), 0.4-ml aliquots were withdrawn, acidified, and frozen. The samples were subsequently assayed for laudanosine.

Atracurium and the monoquaternary alcohol

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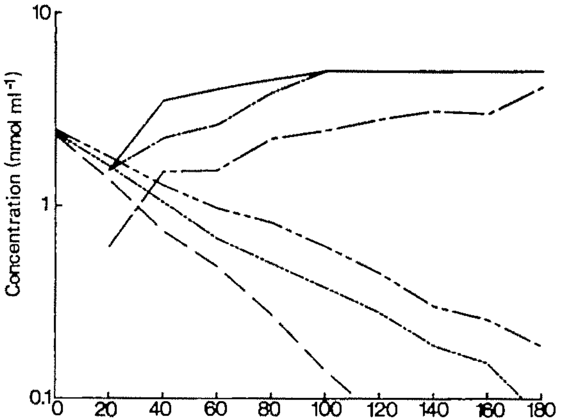

FIG. 1. Logarithm of atracurium and laudanosine concentration (nmol ml^{-1}) over time in a variety of mediums at pH 7.3 and 37 °C. Atracurium (bottom group) concentrations in plasma (— — —), plasma:buffer (1:1) (—·—·—), and in buffer alone (—·—·—·—). Laudanosine (top group) concentrations in plasma (————), plasma:buffer (— — — —), and buffer alone (—·—).

TABLE I. *The inactivation of atracurium and generation of laudanosine at 37 °C and pH 7.3 in several mediums. The laudanosine:atracurium molar ratio was calculated from the laudanosine concentration (nmol ml^{-1}) at the indicated time and the atracurium concentration (nmol ml^{-1}) at time zero*

Medium	$T_{\frac{1}{2}}$ (min)	Laudanosine:atracurium molar ratio 20 min	60 min	120 min	180 min
Sörensen buffer	58	0.2	0.6	1.1	1.7
Plasma:buffer (1:1)	33	0.6	1.1	2.0	2.0
Plasma	21	0.7	1.7	2.0	2.0
Plasma+DIFP	62	0.2	0.6	1.1	1.7

were provided by Burroughs Wellcome Co., Research Triangle Park, North Carolina, U.S.A. High pressure liquid chromatography of the monoquaternary alcohol revealed four distinct components. From these chromatograms we estimated that about 50% of the material was the alcohol. The components had relative retention times different from laudanosine. Atracurium and laudanosine had single peaks on the chromatograms. Laudanosine was purchased from the Aldrich Co., Chicago. Diisopropylfluorophosphate was obtained from Sigma Chemical Co., St Louis, Mo, U.S.A. Since other potential metabolites of atracurium were not available to us, their quantitative analysis and, thus, the quantitative evaluation of their role(s) in the degradation of atracurium was not possible.

RESULTS

Immediately after mixing with the previously described buffer or plasma solution, the mean atracurium concentration was 2.4 nmol ml^{-1}; no laudanosine was detectable. Atracurium was degraded in Sörensen buffer, 1:1 dilution of buffer and plasma, and in pooled plasma at a linear rate (fig. 1). The degradation half-life of atracurium was significantly shorter in plasma than in diluted plasma or buffer (fig. 1, table I). Addition of DIFP to plasma but not to buffer markedly prolonged the half-life of atracurium.

The laudanosine concentration increased in a biphasic fashion in buffer or plasma (fig. 1). The molar ratios of the laudanosine concentration (nmol ml^{-1}) to the atracurium concentration (nmol ml^{-1} at time zero) at 20, 40, 60 and 180 min are listed in table I. At 180 min about 4.8 nmol ml^{-1} of laudanosine was generated from atracurium 2.4 nmol ml^{-1} (that is, each nmol of atracurium generated 2 nmol of laudanosine). At the earlier time periods (20, 40, 60 min) higher concentrations of laudanosine were generated in plasma than in the other solutions; this is reflected in the higher molar ratios of laudanosine:atracurium at each time.

Laudanosine was generated from the monoquaternary alcohol in both buffer and in plasma. In the buffer solution laudanosine 0.20, 0.28, 0.50, 0.85 and 1.20 nmol ml^{-1} was generated at 20, 40, 60, 120 and 180 min, respectively. In plasma, laudanosine 0.28, 0.63, 0.94, 1.17 and 1.59 nmol ml^{-1} was generated at 20, 40, 60, 120 and 180 min, respectively. DIFP decreased the laudanosine concentration in plasma at any given time to that noted in buffer; DIFP had no effect on laudanosine generation in buffer. We could not quantitate the molar concentration of quaternary alcohol at any time.

DISCUSSION

Under physiological conditions atracurium is continually undergoing inactivation. Redistribution and elimination of atracurium also play a role in *in vivo* kinetics. Although a dual pathway for inactivation of atracurium has been proposed (Hughes and Chapple, 1981; Neill and Chapple,

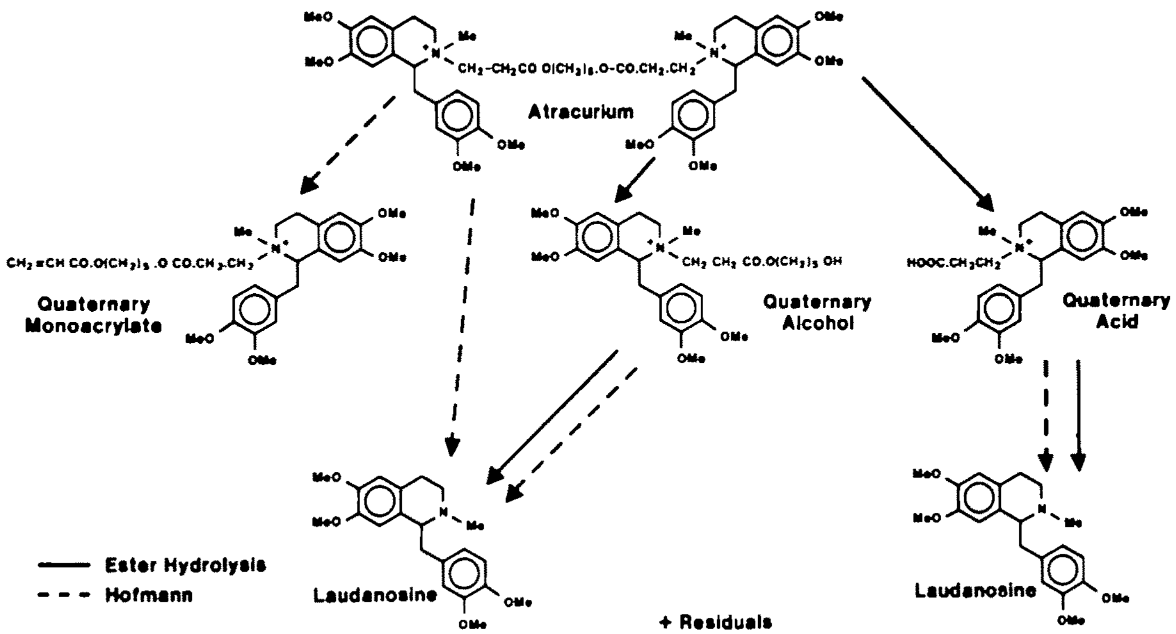

FIG. 2. Proposed pathways of atracurium degradation and metabolism. Solid line represents ester hydrolysis and dashed line the Hofmann reaction.

1982), the role of each metabolic pathway is unclear. This study demonstrates that, at physiological pH and temperature, atracurium is more rapidly degraded and inactivated in plasma than in buffer. Specifically, the half-life of atracurium is about threefold longer in buffer than in plasma (at the same pH and temperature). Dilution (1:1) of plasma constituents with buffer increases the half-life of atracurium several-fold. Likewise, diisopropylfluorophosphate, a potent esterase inhibitor, increases the half-life of atracurium in plasma to that in buffer alone. On the other hand, DIFP has no influence on atracurium degradation in buffer. Most likely, non-specific aliesterases facilitate the hydrolysis of atracurium (Merrett, Thompson and Webb, 1983). Pseudocholinesterase activity has no effect, *per se*, on the inactivation of atracurium (Merrett, Thompson and Webb, 1983). We have made no attempt to characterize further the esterases responsible for the degradation of atracurium. The degradation of atracurium in plasma is inhibited by both acidosis and hypothermia (Merrett, Thompson and Webb, 1983; Stiller, Brandom and Cook, 1984).

Non-enzymatic degradation (Hofmann elimination) of 1 molecule of atracurium can produce a molecule of laudanosine and 1 molecule of monoacrylate–laudanosine component; the monoacrylate–laudanosine component can be further degraded to another molecule of laudanosine and the residual acrylate bridge component (Neill and Chapple, 1982). Thus, in theory, each atracurium molecule can be degraded by Hofmann elimination to 2 molecules of laudanosine. On the other hand, it has been proposed that the ester hydrolysis pathway produces a monoquaternary alcohol and a monoquaternary acid (Neill and Chapple, 1982). These routes of degradation have generally been described as dual but separate pathways. Our data demonstrate that laudanosine is the major end-product of both pathways and that the laudanosine : atracurium molar ratio increases more rapidly in plasma than in buffer. We estimate that, at 40 min, two-thirds of atracurium is degraded by ester hydrolysis and one-third by the Hofmann reaction. We were somewhat surprised by these findings.

Neill and Chapple (1982) proposed that the monoquaternary alcohol, a product of the ester hydrolysis of atracurium, can be degraded by Hofmann elimination to laudanosine or alternatively hydrolysed to the quaternary acid. They also propose that the quaternary monoacrylate from the Hofmann reaction can be hydrolysed to the quaternary alcohol. In addition, we believe laudanosine can be formed from the quaternary acid. Our data suggest that ester hydrolysis and Hofmann elimination degrade the quaternary alcohol and acid to laudanosine, and that the ester hydrolysis is more important. Thus, the quaternary alcohol and acid are important bridges between the two proposed pathways.

The formation of laudanosine from atracurium is biphasic in both plasma and buffer. Laudanosine is generated from atracurium and from intermediate products (the monoquaternary alcohol and acid and quaternary monoacrylate) (fig. 2) via several pathways; the rates of these reactions may differ. For example, the rate of degradation of atracurium to laudanosine and the monoacrylate–laudanosine component may differ from the rate of degradation of the monoacrylate–laudanosine component to laudanosine and the acrylate component. Likewise, the rate of formation of the quaternary alcohol from atracurium and the formation of laudanosine from the quaternary alcohol may vary. To clarify these kinetic issues or to clarify the stoichiometry of these pathways, one would need to first develop sensitive assays for the many metabolites of atracurium. Since these intermediate metabolites of atracurium are not readily available in pure form, we were unable to perform such studies.

Although ester hydrolysis is clearly the major pathway for the degradation of atracurium, severe liver failure or renal failure has little or no effect on atracurium kinetics (Ward and Neill, 1983; Cook et al., 1984). In patients with profound liver failure associated with severe hypoproteinaemia and, hence, severely limited esterases or in patients poisoned with potent esterase inhibitors, the duration of atracurium might be prolonged; studies of the kinetics of atracurium have not been performed in such patients. However, even in the absence of non-specific esterases (as in buffer solution) atracurium is degraded by Hofmann elimination. This feature of spontaneous degradation was a prime consideration in the development of atracurium (Stenlake et al., 1983). Hofmann elimination is, thus, a unique "safety net" in the use of atracurium in patients with severely impaired liver or renal function.

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INTERACTION OF MIDAZOLAM WITH TWO NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN THE RAT *IN VIVO* SCIATIC NERVE–TIBIALIS ANTERIOR MUSCLE PREPARATION

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SUMMARY

Studies of the possible interactions between the water-soluble benzodiazepine, midazolam, and two non-depolarizing neuromuscular blocking drugs, vecuronium and tubocurarine, were performed in the rat in vivo *sciatic nerve–tibialis anterior muscle preparation. Midazolam 0.5 and 5 mg kg^{-1} caused 17% and 34% depression of the twitch height, respectively, once a steady-state blockade of the twitch height had been induced by vecuronium. The potentiation of the tubocurarine steady state blockade by midazolam 5 mg kg^{-1} was quantitatively equal to that of vecuronium, but was slower in onset. The buffer solvent of midazolam 5 mg kg^{-1} did not change the steady-state blockade of vecuronium. Midazolam 5 mg kg^{-1} caused a shift to the left of the cumulative dose–response curves of vecuronium.*

Considerable controversy exists in the literature concerning the interaction between benzodiazepines and neuromuscular blocking drugs (see review by Haefely and colleagues (1981)). In this regard diazepam has been studied almost exclusively, and was shown not to potentiate non-depolarizing drugs in the majority of *in vivo* investigations in rats and cats (Crankshaw and Raper, 1968; Dretchen, Ghoneim and Long, 1971; Webb and Bradshaw, 1973; McIndewar and Marshall, 1981). However, Vergano and co-workers (1969), using the isolated frog sciatic nerve–gastrocnemius muscle preparation, and Cheymol and associates (1967), using the rabbit sciatic nerve–tibialis anterior muscle preparation, demonstrated that diazepam did potentiate the effects of some non-depolarizing neuromuscular blocking drugs.

Like diazepam, most benzodiazepines used in clinical practice are poorly water-soluble and contain organic solvents which are not pharmacologically inert (Crankshaw and Raper, 1971). For example, the pure solvent of diazepam in Valium has been found to antagonize the response to non-depolarizing neuromuscular blocking drugs in animal *in vivo* nerve–muscle preparations (Dretchen, Ghoneim and Long, 1971; Webb and Bradshaw, 1973).

Midazolam is a newer benzodiazepine derivative. Its hydrochloric acid is very stable in water buffered at pH < 4, and its pharmacological potency in the rat is similar to that of diazepam (Pieri et al., 1981). This study investigated the effect of the i.v. administration of midazolam, in sedative doses, on the action of two non-depolarizing neuromuscular blocking drugs, vecuronium and tubocurarine, in the rat sciatic nerve–tibialis anterior muscle preparation.

MATERIALS AND METHODS

Wistar rats, weighing 250–430 g, were anaesthetized with pentobarbitone sodium 60 mg kg^{-1} i.p. Both jugular veins were cannulated with polyethylene catheters for drug administration. Arterial pressure (carotid artery) was recorded on a Grass polygraph. Tracheotomy was performed and ventilation with 50% nitrous oxide in oxygen

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was controlled mechanically to achieve Pa_{CO_2} 4–4.5 kPa. Arterial blood-gas tensions were monitored to ensure normoventilation. Rectal temperature and the temperature of the prepared muscle were measured and maintained between 37 and 38 °C by means of a thermostatically-controlled heating pad under the animal and a heating lamp on the muscle. The tendon of the left anterior tibialis muscle was freed, sectioned and connected to an FT 03 force displacement transducer. The sciatic nerve was cut and the distal end stimulated by supramaximal rectangular (current) single stimuli of 0.2 ms duration at 0.1 Hz through a bipolar electrode. A resting tension of 20 g was applied to the muscle. The resulting twitch tension was recorded on the Grass polygraph. Anaesthesia was maintained by a continuous infusion of pentobarbitone sodium 9–18 mg kg^{-1} h^{-1}.

Two investigations were performed: in the first the effect of midazolam on the twitch height was determined in the presence of steady-state neuromuscular blockade. In most of these studies vecuronium was administered i.v. by a constant infusion to achieve approximately 50 % blockade of the original twitch height. In a few studies tubocurarine was administered similarly. In control studies ($n = 5$) the stability of the neuromuscular blockade produced by vecuronium was verified. When the steady-state depression of the twitch height (of about 50 %) was constant for at least 15 min, the rate at which vecuronium was infused was kept constant for 45 min and the change of twitch height measured over this period. The stability of a tubocurarine-induced steady state neuromuscular block was assessed similarly ($n = 5$).

In six rats the buffer solvent of midazolam in Dormicum (NaCl 5 mg, benzylalcohol 10 µl, 1N HCl 28 µl, 1N NaOH to achieve pH 3.3 ± 0.1, water 1 ml) was injected i.v. once the steady-state blockade had been constant for at least 15 min. The amount of solvent used was equal to that present in midazolam 5 mg kg^{-1}.

In six rats midazolam 0.5 mg kg^{-1} was administered i.v. as a bolus over 2 min once the blockade had been constant for 15 min. In 15 other rats, midazolam 5 mg kg^{-1} was administered similarly.

In six rats a constant degree of neuromuscular blockade was produced by an i.v. infusion of tubocurarine and the effect of midazolam 5 kg mg^{-1} measured.

In all these studies, the resultant percentage change in twitch height, from its steady-state value, was measured for 45 min from the injection of midazolam or solvent, while the infusion of the neuromuscular blocking drug was continued. Student's t test was used to assess the statistical significance of the resultant maximal changes in twitch height in comparison with the changes in control steady state. In the 15 rats receiving midazolam 5 mg kg^{-1}, mean arterial pressures were monitored at 2-min intervals and the changes were analysed statistically by Student's t test for paired data.

In the second group of investigations, cumulative dose–response curves for vecuronium were established 15 min after the administration of midazolam 5 mg kg^{-1} i.v. in eight rats and compared with control dose–response curves in eight other rats anaesthetized similarly, but not receiving midazolam. Incremental doses of vecuronium were given when the previous dose had achieved its maximal effect; that is, when two consecutive twitches of equal height were observed. This was always carried out with two investigators to co-ordinate the observation of twitches and the injection of vecuronium. The dose–response curves were analysed using the model in which the percentage blockade is described as a normal probability integral function of the dose of neuromuscular blocker in a linear scale (Robertson et al., 1983). The mean ED_{50} (dose expected to give 50 % block of the twitch height) and σ/ED_{50} (slope of the curve) were determined for both groups of dose–response curves (control–vecuronium and midazolam–vecuronium).

Student's t test for unpaired data was used for statistical analysis and $P < 0.05$ was considered as the level of significance.

RESULTS

Steady state studies

Once a steady-state depression of the twitch height of at least 15 min duration had been achieved with vecuronium, the mean deviation of the twitch height during the next 45 min of infusion was maximally +4.1 % (SEM ± 2.6) from the twitch height at constant blockade. During control steady-state blockade with tubocurarine the mean deviation varied between +1.75 % (4.5) at 25 min and −5.2 % (2.5) at 60 min. This proved that the model was stable. Tracings of single control experiments of steady state neuromuscular block-

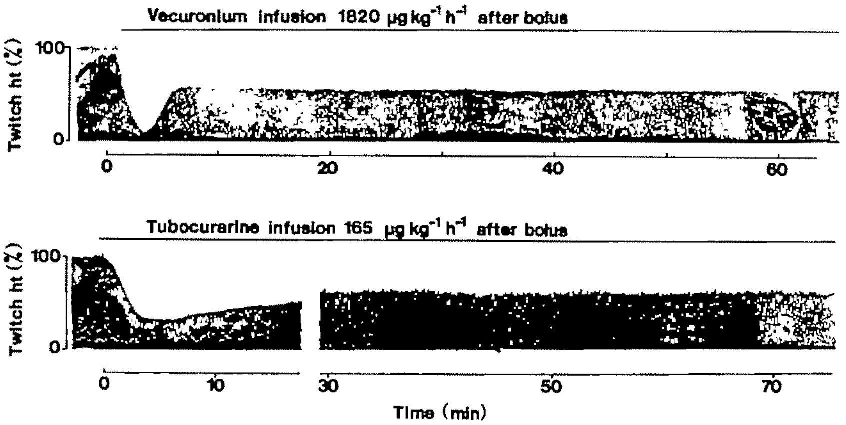

FIG. 1. Representative records of single control studies in which steady-state neuromuscular blockade was induced and maintained with constant infusions of vecuronium or tubocurarine.

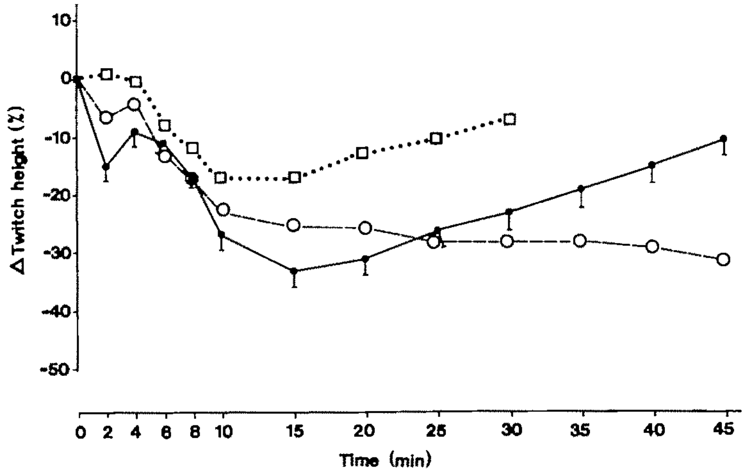

FIG. 2. Effect of midazolam on a steady-state blockade of the twitch height of vecuronium or tubocurarine in the rat *in vivo* sciatic nerve–tibialis anterior muscle preparation. The mean changes in percentage from the twitch height at steady-state blockade after the injection of midazolam i.v. (= time 0) are shown. SEM are shown only for the effect of midazolam 5 mg kg^{-1} on a vecuronium-induced blockade, for reasons of clarity. □ = Midazolam 0.5 mg kg^{-1} on a vecuronium blockade ($n = 6$); ● = midazolam 5 mg kg^{-1} on a vecuronium blockade ($n = 15$); ○ = midazolam 5 mg kg^{-1} on a tubocurarine blockade ($n = 6$).

ade with vecuronium and tubocurarine are shown in figure 1.

When the solvent of midazolam was tested, the resultant changes in twitch height were negligible (mean maximal change = +2.1%) in a 30-min period. With midazolam 0.5 mg kg^{-1} there was an additional depression of the twitch height of 17% (3) from the value reached at steady-state blockade with vecuronium. This potentiation was maximal at 15 min after injection and was significant ($P = 0.004$). With midazolam 5 mg kg^{-1} a 34% (4) additional depression from the twitch height at steady state blockade with vecuronium occurred at 15 min after injection and returned to 11% (5) at 45 min (fig. 2). The change of the twitch height at 15 min was significant when compared with the control as well as with the change after the administration of the solvent ($P < 0.001$). Midazolam 5 mg kg^{-1} caused a significantly higher potentiation of the vecuronium-induced steady-state blockade than did midazolam 0.5 mg kg^{-1}. When midazolam 5 mg kg^{-1} was administered in

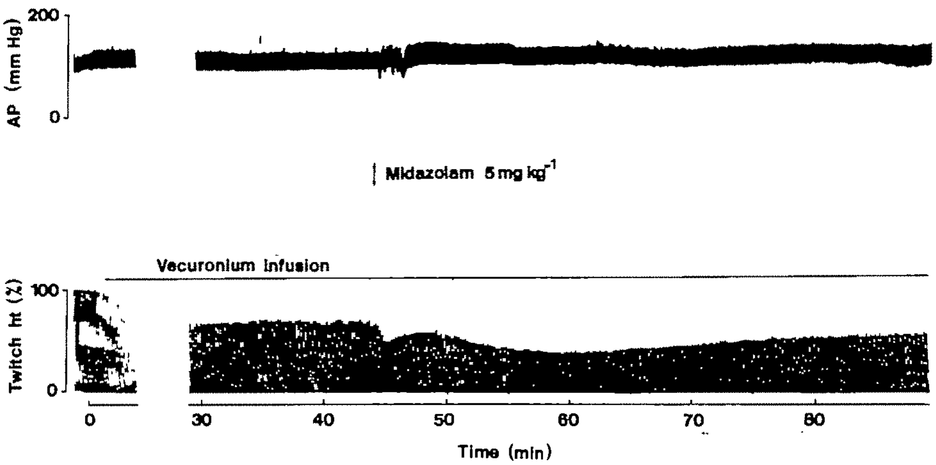

FIG. 3. Representative record showing steady-state blockade with vecuronium. At the arrow midazolam 5 mg kg^{-1} was injected i.v. while the infusion of vecuronium was continued. Note that the depression of the twitch height after midazolam showed a biphasic pattern.

association with a tubocurarine-induced steady-state blockade of twitch height, significant potentiation occurred. The maximal percentage depression from the twitch height at steady-state was 33 % (8) and was only reached 45 min after i.v. injection (fig. 2). Without neuromuscular blocking drugs, midazolam 5 mg kg^{-1} caused no decrease of the twitch height over a 60-min period. Indeed, during the first 15 min there was a small but insignificant increase in the twitch height in most animals. The mean percentage blockade of the twitch height at steady state was 51.8 % (2.0) for all the trials. No significant differences were observed in the depths of the steady-state blockade between the subgroups.

The mean arterial pressure in the 15 rats receiving midazolam 5 mg kg^{-1} plus vecuronium decreased significantly (from 115 to 90 mm Hg) during the first 2 min after the injection of midazolam, but then returned and stabilized at its baseline value. A representative record of a trial with midazolam 5 mg kg^{-1} and vecuronium is shown in figure 3. Note that the depression of the twitch height followed a biphasic pattern.

Cumulative dose–response curves

The dose–response curve of vecuronium was shifted to the left in association with midazolam 5 mg kg^{-1}, which dose decreased the ED_{50} of vecuronium significantly from 297 (36) to 192 (28) µg kg^{-1}. The slope of the curve was not altered significantly (fig. 4).

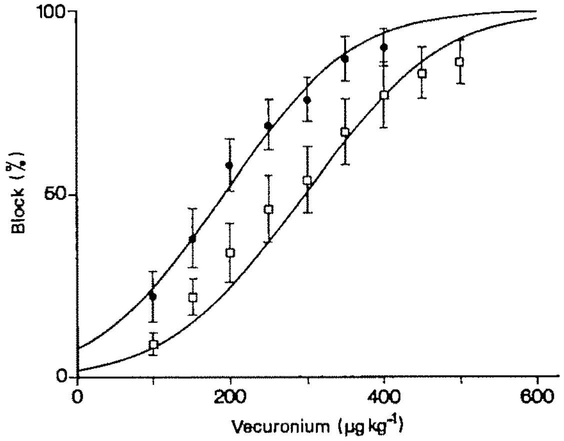

FIG. 4. Cumulative dose–response curves for vecuronium in control rats (□) ($n = 8$) and in other rats 15 min after midazolam 5 mg kg^{-1} (●) ($n = 8$). The bars represent SEM.

DISCUSSION

In rats, midazolam and diazepam are almost equipotent in most pharmacological tests. The i.v. dose of midazolam which causes sedation and "muscle relaxation" in the rat is 5 mg kg^{-1} (Pieri et al., 1981). This is in agreement with i.v. sedative doses of diazepam in the rat reported by others (Ducksook and Dobkin, 1973; Carlsson et al., 1976).

The vecuronium- and tubocurarine-induced steady-state depression of the twitch height was stable over a period of at least 30–45 min. A constant infusion of a non-depolarizing neuromuscular blocking drug is useful in the rat sciatic nerve–tibialis muscle preparation for studies on interactions, as has been demonstrated by other investigators (Miller et al., 1978; Krieg et al., 1980). This is especially true for vecuronium, since it does not show evidence of cumulation, either in effect or in plasma concentration (Agoston et al., 1980).

Our results show that neuromuscular blockade produced by vecuronium was potentiated by sedative doses of midazolam in the rat. This potentiation was attributable to midazolam and not to the solvent. The potentiation was dose-dependent and time-related. With tubocurarine the time-course of the potentiation was different: slower in onset and prolonged in duration. However, we cannot exclude the possibility that this prolonged potentiation of tubocurarine was caused in part by some cumulation of tubocurarine.

Several mechanisms could contribute to the interactions between neuromuscular blocking agents and other drugs (Waud, 1981). Since the dose–response curve of vecuronium was shifted to the left and did not deviate significantly from parallelism after midazolam 5 mg kg^{-1}, this provides some evidence for an interaction at the level of the neuromuscular junction or the muscle, or both. However, other mechanisms of interaction (protein binding, elimination kinetics and haemodynamic changes) must be studied further. Since the sciatic nerve was cut, spinal reflex mechanisms were excluded. The different time-courses of the interactions of midazolam with vecuronium and tubocurarine may be related to differences in the activity of the two non-depolarizing blocking drugs at different receptors in the neuromuscular junction. The response of the arterial pressure to midazolam suggests that this is not the main mechanism of interaction, although benzodiazepines may change the local distribution of blood to muscles without any significant change in arterial pressure.

The fact that the solvent of midazolam had no effect has ensured a reliable assessment of the interaction of midazolam *per se* with these neuromuscular blocking drugs. The question remains whether midazolam behaves differently from other benzodiazepines in regard to the peripheral interaction with non-depolarizing neuromuscular blocking drugs. This can only be answered in interaction studies with different benzodiazepines and by thoroughly assessing the effects of other solvents which can markedly influence the effects of the benzodiazepines themselves (Crankshaw and Raper, 1971; Dretchen, Ghoneim and Long, 1971; Webb and Bradshaw, 1973). The solvent of commercial diazepam (Valium) and some other injectable benzodiazepines may well obscure possible potentiating effects of the active substances. Studies in the rat *in vitro* phrenic nerve–hemidiaphragm preparation showed differences in the response of the twitch contraction to several benzodiazepines (Driessen et al., 1984).

In the present study, considerable variation was observed in the potentiating effect of midazolam on non-depolarizing neuromuscular blocking drugs. Variability of action is common with several benzodiazepines: File (1982) found profound variability in some responses to benzodiazepines in rats without pharmacokinetic differences. In practice, variability means that in some instances unexpectedly marked potentiation may occur, and this emphasizes the need for further investigations of this kind of interaction. It may be worth noting in the light of our studies that Feldman and Crawley (1970) observed prolonged postoperative muscle weakness after combined use of diazepam and tubocurarine in patients.

The neuromuscular function measured with the methods of evoked isometric twitch contractions has a "large margin of safety" (Paton and Waud, 1967). When this margin is decreased by different conditions (myasthenia gravis; hypokalaemia; concomitant use of some antibiotic drugs; liver or kidney dysfunction) vigilance and monitoring are necessary in the use of neuromuscular blocking drugs in combination with benzodiazepines.

In conclusion, the significant potentiation of vecuronium and tubocurarine by midazolam 0.5 and 5 mg kg^{-1} justifies further studies to compare the effects of other injectable formulations of benzodiazepines and their solvents. Since extrapolation of the results to man is difficult, human studies with clinically-used benzodiazepines should be undertaken.

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EFFECT OF MEPTAZINOL ON NEUROMUSCULAR TRANSMISSION IN THE ISOLATED RAT PHRENIC NERVE–DIAPHRAGM PREPARATION*

S. K. STRAHAN, B. J. PLEUVRY AND C. Y. MODLA

SUMMARY

Meptazinol has been shown to have significant effects on neuromuscular transmission in the isolated rat phrenic nerve–diaphragm preparation. The response of the preparation to indirect electrical stimulation was increased in a concentration-dependent manner by meptazinol hydrochloride 2–32 $\mu g\ ml^{-1}$. Meptazinol 0.5–2 $\mu g\ ml^{-1}$ antagonized the effects the tubocurarine on this preparation, and in concentrations of 1 $\mu g\ ml^{-1}$ and greater, potentiated suxamethonium. These effects were similar to those obtained with neostigmine and it was demonstrated that meptazinol had significant anti-cholinesterase activity in the concentrations used. Inhibition of cholinesterase with ecothiopate revealed a neuromuscular blocking activity of meptazinol in concentrations as low as 0.25 $\mu g\ ml^{-1}$.

Meptazinol is an analgesic agent which combines agonist and antagonist opioid analgesic activity, and cholinergic analgesic activity (Bill et al., 1983). Moreover, meptazinol has been shown to facilitate the action of acetylcholine which has been released by electrical stimulation of the isolated guineapig ileum (Stephens, Waterfall and Franklin, 1978). The present study was designed to determine whether meptazinol modified neuromuscular transmission at the skeletal neuromuscular junction *in vitro* and, if so, whether it could modify the action of neuromuscular blocking agents. To gain some preliminary information about the possible mechanisms underlying the pharmacological effects of meptazinol, comparisons have been made with neostigmine.

MATERIALS AND METHODS

Male Sprague–Dawley rats were killed by a blow to the head and the two phrenic nerve–hemidiaphragm preparations (Bulbring, 1946) dissected out. The preparations were arranged for indirect stimulation by the application of rectangular electrical pulses to the phrenic nerve (0.5 ms, 0.1 Hz and a voltage greater than that required to produce a maximal twitch) and for direct stimulation (5 ms, 0.1 Hz and a voltage greater than that required to produce a maximal twitch) of the muscle. The muscle was set up at a resting tension of 4 g and the whole preparation was immersed in Krebs–Henseleit solution at 37 °C and bubbled with 5% carbon dioxide in oxygen. Contractions of the muscle were recorded using an isometric transducer connected to a Grass 79C polygraph.

Preliminary studies showed that meptazinol (as the hydrochloride) was difficult to wash off the preparation reliably and, thus, preparations were exposed to increasing concentrations of meptazinol hydrochloride in a cumulative manner. In order to determine whether prior exposure to low concentrations of meptazinol influenced the responses to subsequent exposures to high concentrations, some preparations were exposed to the high concentrations of meptazinol only.

When either tubocurarine or suxamethonium was applied to the stimulated preparations a contact time of 5 min was used, followed by at least

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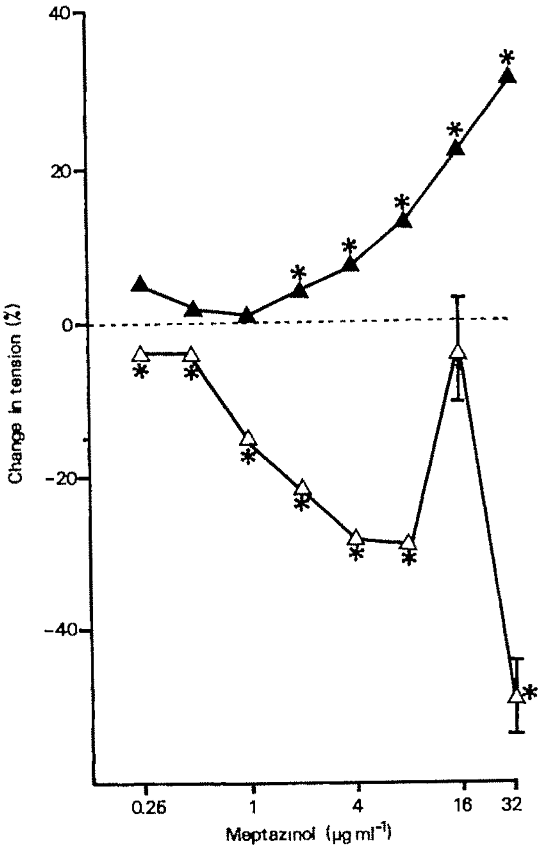

FIG. 1. Effect of meptazinol hydrochloride on the contraction of the diaphragm muscle in response to electrical stimulation of the phrenic nerve in control preparations (▲) and in preparations treated with ecothiopate iodide 96 ng ml^{-1} (△). Mean values ±SEM ($n = 6$). *Significant change from premeptazinol values ($P < 0.05$).

three washes over the subsequent 15 min. Concentration effect curves for either tubocurarine or suxamethonium were obtained before the administration of meptazinol hydrochloride or neostigmine methylsulphate, and then with increasing concentrations of the two agents. Preparations were pretreated with either meptazinol hydrochloride or neostigmine methylsulphate for 15 min before the addition of the neuromuscular blocking agents. Subsequently, the preparations were washed in Krebs–Henseleit solution containing the modifying agents. The EC_{50} values for suxamethonium and tubocurarine in the presence of modifying agents were compared with EC_{50} values obtained from time-matched control preparations not treated with meptazinol hydrochloride or neostigmine methylsulphate.

Preparations treated with ecothiopate iodide 96 µg ml^{-1} (an "irreversible" anticholinesterase) were left for a minimum of 30 min before the addition of any other drug. Meptazinol hydrochloride was added as single concentrations and then washed off. The contact time was sufficient to allow a maximum response to meptazinol—5–10 min.

Measurement of cholinesterase inhibition

The cholinesterase activity of homogenates of rat phrenic nerve–diaphragm preparations was assayed using the method described by Ellman and colleagues (1961). Acetylthiocholine was hydrolysed by the cholinesterase in the tissue and the rate of hydrolysis was measured as the increase in the yellow colour produced by the interaction of thiocholine with the dithiobisnitrobenzoate ion.

Various concentrations of meptazinol hydrochloride or neostigmine methylsulphate were added to the cuvette and the inhibition of cholinesterase activity measured.

Unless otherwise stated, results are expressed as mean values ±SEM of not less than six experiments. Significance was assessed using the Student's *t* test.

RESULTS

Meptazinol 2–32 µg ml^{-1} caused an increase in the muscle contraction in response to indirect electrical stimulation (fig. 1); meptazinol 64 µg ml^{-1} caused an initial increase in contraction followed by a decrease to undetectable values at 5 min. The muscle contraction in response to direct stimulation was unaffected by these concentrations of meptazinol.

In control preparations the EC_{50} values for both tubocurarine and suxamethonium decreased slightly with time (table I). Meptazinol 0.5–2 µg ml^{-1} significantly increased the EC_{50} for tubocurarine, a result indicative of antagonism. This effect was lost with meptazinol 4 µg ml^{-1}. A similar result was obtained when 4 µg ml^{-1} was added to the tissue first. In contrast, meptazinol caused a concentration-dependent decrease in EC_{50} for suxamethonium. Neostigmine methylsulphate had qualitatively similar effects on the neuromuscular blockade produced by tubocurarine and suxamethonium (table II), although antagonism of tubocurarine still occurred with concentrations of neostigmine up to 2 µg ml^{-1}.

TABLE I. *Effect of meptazinol hydrochloride on the response of the indirectly stimulated rat phrenic nerve–diaphragm preparation to tubocurarine and suxamethonium* : EC_{50} *(μg ml^{-1}) geometric mean (±SEM)* (n = 6). *Time-matched control preparations were not treated with meptazinol.* **Significantly different from time-matched control* ($P < 0.05$)

	Tubocurarine		Suxamethonium	
Meptazinol concn (μg ml^{-1})	Test preparation	Time-matched control	Test preparation	Time-matched control
0	0.98 (+0.06 −0.06)	0.98 (+0.06 −0.07)	8.12 (+0.19 −0.18)	7.58 (+0.18 −0.17)
0.25	1.07 (+0.13 −0.12)	0.89 (+0.09 −0.08)	7.24 (+0.34 −0.32)	7.41 (+0.17 −0.17)
0.5	1.12* (+0.11 −0.12)	0.85 (+0.09 −0.08)		
1.0	1.20* (+0.03 −0.02)	0.89 (+0.06 −0.06)	4.07* (+0.29 −0.27)	6.61 (−0.31 −0.30)
2.0	1.12* (+0.08 −0.07)	0.81 (+0.08 −0.07)		
4.0	0.89 (+0.06 −0.06)	0.79 (+0.10 −0.09)	1.74* (+0.16 −0.14)	6.17 (+0.44 −0.42)

TABLE II. *Effect of neostigmine methylsulphate on the response of the indirectly stimulated rat phrenic nerve–diaphragm preparation to tubocurarine and suxamethonium* : EC_{50} *(ng ml^{-1}) geometric mean (±SEM)* (n = 6). *Time-matched control preparations were not treated with neostigmine.* **Significantly different from time matched controls* ($P < 0.05$)

	Tubocurarine		Suxamethonium	
Neostigmine concn (ng ml^{-1})	Test preparation	Time-matched control	Test preparation	Time-matched control
0	1.25 (+0.12 −0.11)	1.26 (+0.12 −0.11)	8.12 (+0.59 −0.53)	7.94 (+0.97 −0.86)
1.0	1.20 (+0.09 −0.08)	1.02 (+0.08 −0.07)		
4.0	1.26 (+0.08 −0.08)	1.02 (+0.08 −0.07)	6.61 (+0.47 −0.44)	7.08 (+0.05 −0.47)
8.0	1.95* (+0.19 −0.18)	1.05 (+0.07 −0.07)		
16.0	2.04* (+0.09 −0.09)	0.91 (+0.07 −0.06)	5.75 (+0.56 −0.50)	6.54 (+0.31 −0.29)
64.0			3.01* (+0.62 −0.49)	5.5 (+0.52 −0.49)

The mean cholinesterase activity of the homogenized male rat diaphragm was 1.33 ± 0.02 mol litre^{-1} min^{-1} $\times 10^{-6}$ per g of tissue. Both meptazinol and neostigmine caused a concentration-dependent inhibition of this activity (fig. 2). The geometric mean EC_{50} for meptazinol was 1.54 (+0.32, −0.26) μg ml^{-1} and the geometric mean EC_{50} for neostigmine was 2.97 (+0.53, −0.45) ng ml^{-1}.

In view of the significant anticholinesterase activity of meptazinol in the concentrations used, its effects on the indirectly stimulated rat phrenic nerve–diaphragm preparation were examined in preparations whose cholinesterase had been inhibited by ecothiopate iodide 96 μg ml^{-1} (83% inhibition on the homogenized preparation). In these circumstances meptazinol caused no increase in the tension of the muscle contraction, but caused significant decreases in tension in concentrations of 0.25 μg ml^{-1} and 1 μg ml^{-1} (fig. 1). The unexpected lack of response of the preparation to meptazinol 16 μg ml^{-1} was a consistent finding.

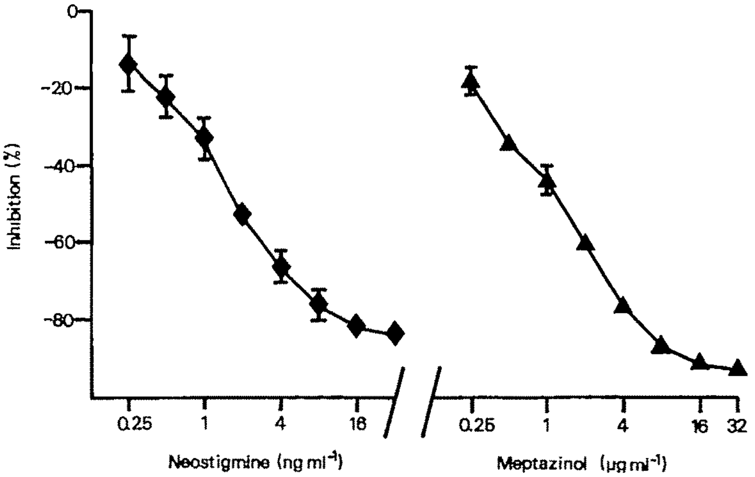

FIG. 2. Inhibition of rat diaphragm cholinesterase by meptazinol hydrochloride (▲) and neostigmine methylsulphate (◆). Mean values ± SEM ($n = 6$).

DISCUSSION

Meptazinol has been shown to antagonize the neuromuscular blocking effects of tubocurarine and to potentiate those of suxamethonium. Qualitatively similar results were seen with neostigmine. The actions and drug interactions of neostigmine on the neuromuscular junction can be adequately explained on the basis of the inhibition of acetylcholinesterase at that site. However, neostigmine may also have presynaptic actions (Blaber, 1963) or direct acetylcholine-like properties (Riker and Wescoe, 1946) which contribute to its actions alone and in the presence of neuromuscular blocking drugs.

This study has shown that meptazinol, like neostigmine, inhibits the cholinesterase present in the rat diaphragm muscle and that this occurred in the same concentration range for meptazinol as that used in the organ bath experiments. This suggests that anticholinesterase activity is important as far as the actions of meptazinol described in this paper are concerned.

Neostigmine inhibited the cholinesterase in the homogenized diaphragm in concentrations which were without obvious effects on neuromuscular transmission in the intact preparation. It is possible that the access of the highly polar neostigmine to cholinesterase is facilitated by homogenization. Tissue disruption may be less important for the lipid soluble meptazinol. However, not all of the effects of meptazinol seen in this study can be attributed to anticholinesterase activity, as high concentrations blocked neuromuscular transmission—an effect not seen with neostigmine in concentrations with comparable anticholinesterase activity. Furthermore, prior inhibition of cholinesterase by ecothiopate, a water soluble organophosphorous "irreversible" anticholinesterase agent (Taylor, 1980), unmasked an inhibitory action of meptazinol on neuromuscular transmission at concentrations as low as 0.25 µg ml^{-1}. No evidence has been gained from this study to determine whether the inhibitory actions of meptazinol are presynaptic or postsynaptic. It is tempting to dismiss the lack of effect of meptazinol 16 µg ml^{-1} on the ecothiopate-treated preparation as an error in methodology. Unfortunately, neither fresh drug dilution nor new preparations produced any evidence that this was the case. An explanation of this finding must await a more detailed study of the actions of meptazinol on the neuromuscular junction.

The lack of antagonism of tubocurarine by meptazinol 4 µg ml^{-1} may be the result of the intrinsic neuromuscular blocking activity of meptazinol overcoming its anticholinesterase activity.

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SISTER CHROMATID EXCHANGES IN CIGARETTE SMOKERS: EFFECTS OF HALOTHANE, ISOFLURANE OR SUBARACHNOID BLOCKADE

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AND E. NIEBUHR

SUMMARY

In a previous study of the potential mutagenic action of isoflurane using the sister chromatid exchange (SCE) test in lymphocytes of surgical patients, it appeared that SCE increased in a group of 11 cigarette smokers, there being no effect in patients who were non-smokers. In the present study, 63 cigarette smokers were examined by the SCE test before and after minor orthopaedic operations undertaken under halothane or isoflurane anaesthesia, or subarachnoid analgesia. No significant changes of SCE were observed, and the risk of having missed a "true" increase of more than 0.6 SCE per cell was less than 1%. It was concluded that, in cigarette smokers, SCE in lymphocytes were unchanged after both general anaesthesia and subarachnoid analgesia, and that there was no indication from the SCE test of a mutagenic action of halothane, or isofurane, in nitrous oxide.

Testing of the potential mutagenic effects of inhalation anaesthetics by the sister chromatid exchange (SCE) test in lymphocytes from patients undergoing surgery has yielded negative responses following anaesthesia with halothane (Husum, Wulf and Niebuhr, 1981a; Holmberg et al., 1982), enflurane (Husum, Wulf and Niebuhr, 1981a) and fluroxene (Husum, Wulf and Niebuhr, 1982a). In a similar study of isoflurane (Husum et al., 1984) there was a negative response in non-smoking patients, whereas SCE increased significantly in a subset of 11 patients who were cigarette smokers—when examined on the day following the operation. It is known that cigarette smokers have increased SCE in lymphocytes in peripheral blood (Lambert et al., 1978; Husum, Wulf and Niebuhr, 1982b), but it is unknown whether cigarette smokers react differently from non-smokers when exposed to potential SCE-inducing agents (Watanabe et al., 1983).

In the present study, the possible SCE-inducing effect of anaesthetic agents was studied in patients who were cigarette smokers. In a total of 63 regular cigarette smokers, SCE was examined before and after surgery under general anaesthesia (with halothane or isoflurane) or in association with subarachnoid analgesia.

PATIENTS AND METHODS

Sixty-three patients aged 18–64 yr (median 35.3 yr) who underwent minor orthopaedic surgery were studied. There were 23 women aged 18–64 yr (median 36.0 yr), and 40 men aged 19–63 yr (median 35.0 yr). All patients were healthy and had received no regular medication before operation. All were regular cigarette smokers, their average daily cigarette consumption being 15.2 cigarettes (range 10–30 cigarettes per day) (table I).

The investigation was approved by the Copenhagen County Ethical Committee. Informed

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TABLE I. *Demographic data for 63 patients in whom sister chromatid exchanges (SCE) were examined before anaesthesia and on the day after the operation*

Treatment group	No. patients	Age (yr)		Cigarettes per day		Duration of anaesthesia (min)		Cigarette consumption between 1st and 2nd sample	
		Median	Range	Median	Range	Median	Range	Median	Range
Halothane	20	34.5	20–64	16.5	10–30	63	35–115	4.0	0–25
Isoflurane	23	35.5	18–63	17.5	10–30	80	30–120	2.8	0–8
Subarachnoid analgesia	20	38.5	19–57	13.7	10–20			4.0	0–8

consent was obtained from all patients at the preoperative visit. The patients were asked to refrain from smoking from the midnight before the operation and for the following 36 h. In all patients premedication consisted of pethidine 1 mg kg^{-1} i.m.

In two of the groups, anaesthesia was induced with either halothane or isoflurane with 67% nitrous oxide in oxygen. Tracheal intubation was necessary in a few patients, but was performed always without the use of myoneural blockers. Pethidine was used to supplement anaesthesia and to provide pain relief in the period after surgery. In a third group, analgesia was produced by the intrathecal injection of 0.5% bupivacaine 4–5 ml.

Venous blood was sampled before the induction of anaesthesia and again on the day after operation. Blood samples were labelled with code numbers so that the investigators were unaware of the time of withdrawal.

The SCE analyses were undertaken using the method described by Wulf (1980). Thirty metaphases were scored for SCE in each specimen, one SCE being counted each time two adjacent segments of one of the chromatids in a chromosome were stained differently.

Statistical methods. Using the approach described previously (Husum, Wulf and Niebuhr, 1981b; Wulf et al., 1984), the sum of SCE in 30 cells from each patient was transformed into a normally distributed variable $y = (\text{sum SCE})^{\frac{1}{2}} + (\text{sum SCE} + 1)^{\frac{1}{2}}$. A two-tailed paired *t* test was used to compare the mean values of the variable *y* in each of the groups of patients before and after the operation. Analysis of variance was used to compare the observations in the three groups.

RESULTS

Before the induction of anaesthesia, the 63 patients had 9.15±0.21 SCE per cell (mean±SEM), and there was no significant difference between the mean SCE values in the three treatment groups (table II). On the day after the operation, the 63 patients averaged 8.94±0.19 SCE per cell; that is,

TABLE II. *Sister chromatid exchanges (SCE) in 63 patients who were cigarette smokers (average 15.2 cigarettes per day) who received halothane* (n = 20), *isoflurane* (n = 23) *or subarachnoid analgesia* (n = 20) *for minor orthopaedic operations. Statistical evaluation of the transformed variable,* y, *indicated no significant differences between the groups before or after the operation (analysis of variance) and no significant changes within the groups (two-tailed* t *test)*

	SCE per cell			$y = (\text{sum SCE})^{\frac{1}{2}} + (\text{sum SCE} + 1)^{\frac{1}{2}}$		
	Mean	Range	SEM	Mean	SEM	*t*
Before halothane	9.02	6.57–12.83	0.33	32.83	0.61	
1st day after op.	8.65	7.00–10.93	0.25	32.17	0.48	1.4472
Before isoflurane	9.12	6.30–12.47	0.29	33.02	0.53	
1st day after op.	9.04	6.40–12.27	0.33	32.84	0.61	0.3812
Before subarachnoid analg.	9.29	6.47–13.53	0.43	33.25	0.70	
1st day after op.	9.15	6.80–12.47	0.38	33.03	0.78	0.4732

SCE had not changed significantly from the corresponding values observed before the induction of anaesthesia in any of the three treatment groups (table II).

DISCUSSION

The possibility of a potential mutagenic action of inhalation anaesthetics has been investigated with the Ames Salmonella assay system (Baden et al., 1977; Waskell, 1978; Baden and Simmon, 1980) and with the SCE test following exposure *in vitro* (White et al., 1979) and *in vivo* (Basler and Röhrborn, 1981; Husum, Wulf and Niebuhr, 1981a, 1982a; Holmberg et al., 1982; Husum et al., 1984).

Increased SCE in lymphocytes has been demonstrated as early as 75 min after the administration of a known SCE-inducing agent (Wulf et al., 1984) and an increased value of SCE following acute exposure is believed to persist for at least 4–16 weeks (Vainio et al., 1981). Therefore, it was reasonable to assume that the design of the present study would allow the detection of any change in SCE which might have been induced during the period of anaesthesia and surgery.

The three study groups were comparable with respect to cigarette consumption and pertinent personal data (table I), and before the operation there were no differences in SCE between the groups (table II). The number of SCE per cell was the same as observed in a previous study of SCE in healthy cigarette smokers (Husum, Wulf and Niebuhr, 1982b).

The duration of anaesthesia was in the same range in both groups receiving general anaesthesia. In the patients receiving subarachnoid analgesia, injection of 0.5% bupivacaine 4–5 ml typically produced sensory blockade up to the lower thoracic segments.

On the day after the operation, there were no significant changes in SCE in any of the three groups (table II), and there were no differences in postoperative SCE values between the three treatment groups. From estimates of the 99% confidence limits from the mean differences between SCE per cell before and after the operation, it appeared that the risk of having missed a "true" increase of more than 0.6 SCE per cell was 1% or less in all the three groups.

This is in contrast to our earlier study on patients anaesthetized with isoflurane (Husum et al., 1984), in which 11 patients who were cigarette smokers (average 10 cigarettes per day) averaged 8.57 ± 0.38 per cell before the operation and 9.38 ± 0.36 SCE per cell on the day after the operation. This increase of 0.81 SCE per cell was significant at the 2% level. The patients were undergoing the same surgical procedures and the anaesthetic procedures were quite similar in the two studies, except that diazepam was used for premedication in the earlier study. We do not believe that the oral intake of a single, large dose of diazepam is a confounding factor since, according to a recent study, SCE is not influenced by such medication (Husum et al., 1985).

We conclude that, in cigarette smokers undergoing minor orthopaedic surgery, SCE in lymphocytes were unchanged after both general anaesthesia and subarachnoid analgesia, and that there was no indication, from the SCE test, of a mutagenic action as a result of anaesthesia with isoflurane, or halothane, in nitrous oxide.

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ABSTAINING FROM CIGARETTE SMOKING HAS NO MAJOR EFFECT ON GASTRIC EMPTYING IN HABITUAL SMOKERS

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SUMMARY

The rate of liquid-phase gastric emptying was determined in seven smokers from the rate of paracetamol absorption after abstaining overnight from cigarettes, and again after smoking two cigarettes within 30 min. There were no significant differences between the maximum paracetamol concentration, the time to reach maximum paracetamol concentration, and the area under the plasma concentration–time curve from 0 to 120 min on the two occasions, indicating that abstaining from cigarette smoking had no major effect on gastric emptying in habitual smokers.

The effect of cigarette smoking on the rate of gastric emptying is controversial. Grimes and Goddard (1978) found that cigarette smoking accelerated the rate at which the liquid component of a test meal left the stomach. In contrast, Harrison and Ippoliti (1979) showed that smoking cigarettes with a high nicotine concentration delayed the gastric emptying of solid food in some subjects, and Ohzeki (1981) also reported that smoking produced a marked delay in emptying. We have investigated the effect of abstaining from cigarettes on the rate of gastric emptying in habitual smokers, using the rate of paracetamol absorption as an indicator of the rate of gastric emptying (Clements et al., 1978; Heading et al., 1973).

SUBJECTS AND METHODS

Seven healthy habitual smokers, aged between 25 and 35 yr, with a daily consumption of 15–25 cigarettes, were studied on two occasions separated by at least 2 weeks. The study was approved by the local Ethics Committee. On the first occasion the subjects were investigated after a night during which they did not take any fluid, food or tobacco. On the second occasion they smoked two cigarettes with a nicotine content 2.0 mg per cigarette within 30 min of the beginning of the study. Each investigation was started by the ingestion of paracetamol 20 mg kg^{-1} dissolved in 200 ml of water and fasting was continued until the end of the study. Samples of venous blood were obtained from an indwelling cannula before, and at 10, 20, 30, 40, 50, 60, 75, 90 and 120 min after, the administration of the paracetamol. Serum was separated and stored at −20 °C until the measurement of serum paracetamol concentration by high pressure liquid chromatography (Knox and Jurands, 1978).

Statistics

Data were compared using Student's t test for paired data. P values less than 0.05 were considered statistically significant.

RESULTS

When the subjects did not smoke, the time to reach peak paracetamol concentrations was 27 ± 3.6 min (mean ± SEM of seven values) (table I). Peak serum paracetamol concentration was 20.1 ± 1.8 $\mu g\ ml^{-1}$ and the area under the plasma concentration–time curve from 0 to 120 min was 1465 ± 74.5 $\mu g\ min^{-1}\ ml^{-1}$. After smoking, the time to reach peak paracetamol concentrations was

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TABLE I. *Time to the maximum concentration* (t_{max}), *the maximum concentration* (C_{max}) *of paracetamol (20 mg kg/body weight) and the area under the curve from 0 to 120 min (AUC) in seven healthy volunteers abstaining from smoking, and smoking*

	t_{max} (min)		C_{max} ($\mu g\ ml^{-1}$)		AUC ($\mu g\ min^{-1}\ ml^{-1}$)	
Subject	No smoking	Smoking	No smoking	Smoking	No smoking	Smoking
1	40	20	14.89	19.20	1958	1566
2	40	20	16.04	17.83	1183	963
3	30	10	22.49	30.03	1513	1705
4	20	75	21.07	12.73	1449	1017
5	20	60	16.53	12.55	1360	1189
6	20	50	20.54	12.54	1450	992
7	20	40	29.01	22.11	1839	1189
Mean ± SEM	27 ± 3.6	39 ± 9.0	20.1 ± 1.8	18.1 ± 6.5	1465 ± 75	1089 ± 186
P	= 0.35		= 0.46		= 0.09	

39.9 ± 9.0 min, and the peak serum paracetamol concentration was 18.1 ± 6.5 $\mu g\ ml^{-1}$. The area under the plasma concentration–time curve was 1089 ± 186 $\mu g\ min^{-1}\ ml^{-1}$.

None of these values was significantly different ($P > 0.05$). The respective 95% confidence limits for the difference between the two occasions were: time to peak paracetamol concentration −66 to 91 min; peak paracetamol concentrations −17.7 to 13.9 $\mu g\ ml^{-1}$.

DISCUSSION

In the present study paracetamol absorption was used as an indicator of the rate of gastric emptying, a method which has been shown to correlate well with other methods used to estimate gastric emptying (Clements et al., 1978). The data indicate that the liquid phase gastric emptying was not significantly changed by abstaining from cigarette smoking, the 95% confidence limits indicating that, at most, cigarette smoking could delay or accelerate liquid phase gastric emptying by about 1 h.

However, gastric emptying was delayed in four, uninfluenced and one and accelerated in two subjects. These different results may reflect the individual variation of gastric emptying, produced by abstaining from smoking.

Cigarette smoking has been shown either to increase (Piper and Raine, 1959) or to have no effect on basal gastric secretion (Cooper and Knight, 1956), and stimulation by pentagastrin has shown similar divergent results (Debas et al., 1971; Wilkinson and Johnson, 1971). Cigarette smoking decreases the gastro–oesophagal pressure and may allow reflux with accompanying risk of pulmonary aspiration, but only within 8 min after the end of smoking (Stanciu and Bennett, 1972; Chattopadhyay, Greaney and Irvin, 1977). Harrison and Ippoliti (1979) showed that smoking cigarettes with a high nicotine content stimulates duodeno–gastric reflux and, therefore, increases gastric volume, but a recent study has shown no effect of smoking before premedication (Adelhøj et al., 1985). Consequently, abstaining from smoking 2 cigarettes during the fasting period does not decrease the risk of pulmonary aspiration during or after anaesthesia.

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EFFECT OF DIAZEPAM ON DRUG ABSORPTION AND GASTRIC EMPTYING IN MAN

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SUMMARY

Paracetamol 20 mg kg^{-1} dissolved in 200 ml of water was given by mouth to seven healthy volunteers, together with a single i.v. dose of diazepam 0.2 mg kg^{-1} or saline 0.04 ml kg^{-1}. This study demonstrated that the rate of paracetamol absorption was not significantly changed by diazepam, indicating that there was no delay in gastric emptying attributable to diazepam per se.

Diazepam decreases apprehension, excitement and autonomic responses (Dundee and Haslett, 1970), and remains one of the most widely used benzodiazepines. Although diazepam is a safe drug (Kanto, 1981), the effect on gastric emptying in man is not clear.

In the present study we determined the effect, if any, of diazepam on gastric emptying in man, using paracetamol absorption as an index of the rate of gastric emptying. Paracetamol is not absorbed to any appreciable extent from the stomach, but is readily absorbed from the upper small intestine. In this way the rate of absorption of paracetamol following oral administration is dependent on the rate of gastric emptying (Heading et al., 1973). Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed that measurement of the rate of paracetamol absorption is a dependable expression of gastric emptying (Clements et al., 1978).

SUBJECTS AND METHODS

Informed consent was obtained from each subject and the experimental study was approved by the local Ethics Committee.

Seven healthy volunteers (four women) (age 23–36 yr, body weight 45–75 kg, height 155–183 cm) were each studied on two occasions in random order with an interval of at least 2 weeks between studies. Diazepam (5 mg ml^{-1}) 0.2 mg kg^{-1} i.v. or physiological saline 0.04 ml kg^{-1} i.v. was given double-blind to each volunteer. On each occasion they were investigated after an overnight fast. Fasting was continued until the end of the investigation.

The subjects remained at rest in bed in a semi-recumbent position and a slow i.v. infusion of physiological saline was established. Immediately after the injection of the test solution (over 2 min) the subjects ingested paracetamol 20 mg kg^{-1} dissolved in 200 ml of water. Venous blood samples were taken from an indwelling cannula before and 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min after the administration of the paracetamol. Serum was separated and stored at −20 °C until measurement of serum paracetamol concentration by high pressure liquid chromatography was performed (Lo and Bye, 1979).

Paracetamol absorption was assessed from the plasma concentrations at each sampling time, the peak paracetamol concentration ($C_{\max}$), the time to reach peak concentration ($t_{\max}$) and the area under the plasma concentration–time curve from 0 to 120 min (AUC).

A paired Student's t test was used; P values less than 0.05 were considered statistically significant.

RESULTS

Mean plasma paracetamol concentrations at each sampling time are given in table I; the individual

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TABLE I. *Mean plasma paracetamol concentrations (±SEM) and* P *values (Student's* t *test) at each sampling time with and without diazepam. Patients received paracetamol 20 mg kg/body weight dissolved in 200 ml water*

	Mean plasma paracetamol concentrations (μg ml^{-1})									
	10 min	20 min	30 min	40 min	50 min	60 min	75 min	90 min	105 min	120 min
Saline ($n = 7$)	6.2±6.2	14.9±8.0	13.9±5.8	14.0±3.2	14.0±3.5	13.9±3.1	11.9±2.6	11.0±2.9	10.3±2.7	10.2±2.2
Diazepam ($n = 7$)	4.3±5.2	9.5±6.5	10.8±5.2	12.4±3.2	11.8±2.7	13.3±3.8	12.4±4.4	11.9±4.0	10.9±4.0	10.4±3.9
P	0.39	0.24	0.38	0.20	0.18	0.71	0.78	0.64	0.70	0.85

TABLE II. *The individual values of the peak serum paracetamol concentration* (C_{max})*, the time from administration of paracetamol to its peak concentration* (t_{max})*, the area under the plasma concentration–time curve from 0 to 120 min (AUC) and* P *values with and without diazepam*

	C_{max} (μg ml^{-1})		t_{max} (min)		AUC (μg min^{-1} ml^{-1})	
Subject	Saline	Diazepam	Saline	Diazepam	Saline	Diazepam
1	14.9	17.8	40	30	1458	1732
2	16.0	20.7	40	30	1182	1461
3	16.5	15.9	20	60	1440	992
4	18.6	20.3	60	75	1355	1573
5	28.3	17.9	20	40	1971	881
6	12.0	10.3	40	40	905	870
7	20.5	18.9	20	20	1448	1429
Mean±SEM	18.1±2.0	16.5±1.5	34.3±5.7	42.1±7.2	1394±122	1277±134
P	0.57		0.30		0.56	

values of C_{max}, t_{max} and AUC are presented in table II.

At no sampling time did the mean paracetamol concentration after the administration of diazepam differ significantly from the mean concentration after saline ($P > 0.05$).

After the administration of the saline, mean C_{max} was 18.1±2.0 μg ml^{-1} (mean of 7 values±SEM), mean t_{max} was 34.3±5.7 min and mean AUC was 1394±122 μg min^{-1} ml^{-1}. After diazepam, mean C_{max} was 16.5±1.5 μg ml^{-1}, mean t_{max} 42.1±7.2 min and mean AUC was 1277±134 μg min^{-1} ml^{-1}. None of these values was significantly different from control ($P > 0.05$).

The respective 95% confidence limits for the differences between the peak paracetamol concentration and the time to peak paracetamol concentration were −3.0 to 8.0 μg ml^{-1} and −12.2 to 27.8 min, respectively.

DISCUSSION

In the present study paracetamol absorption was used as an index of gastric emptying. This method has been demonstrated to correlate well with other methods used to estimate gastric emptying (Clements et al., 1978).

The study demonstrated that the absorption of paracetamol was not altered significantly by a single i.v. dose of diazepam 0.2 mg kg^{-1}, and would indicate that gastric emptying was not changed significantly by diazepam.

The patterns of gastric emptying were similar in the seven subjects. After both diazepam and placebo, the absorption of the paracetamol seemed to follow a first-order process and gastric emptying was either type 1 or type 2 as classified by Clements and colleagues (1978). However, gastric emptying was delayed slightly in two subjects (No. 3 and No. 5) after diazepam i.v., and this may reflect small individual variations in the rate of gastric emptying produced by diazepam.

Paracetamol absorption was rapid in seven patients awaiting elective general anaesthesia who received diazepam 10 mg i.m. as premedication (Todd and Nimmo, 1983) and paracetamol concentrations from 15 to 90 min after diazepam administration were almost identical to those obtained in eight healthy volunteers who were not receiving diazepam after the same dose of paracetamol (Nimmo and Prescott, 1978). Paracetamol absorption was also rapid 2 weeks after minor surgery on the extremities in patients who had received diazepam 15 mg by mouth (Adelhøj et al., 1984; Petring et al., 1984). However, the present study differs from these studies in a number of ways. First, we gave a larger dose of diazepam than Todd and Nimmo (1983) and, furthermore, we gave the diazepam i.v. Diazepam is fairly rapidly and almost completely absorbed after oral ingestion (Bellatunono et al., 1980), but the absorption depends on gastric emptying (Gamble et al., 1976). After i.m. injection, absorption of diazepam is slow and erratic, possibly because of crystallization at the injection site, resulting in peak plasma concentrations which are lower than after oral administration (Kanto, 1975). Moolenaar and co-workers (1980) showed that a peak concentration of 375 ± 79 ng ml^{-1} was reached 95 ± 39 min after diazepam 10 mg i.m. in nine volunteers, a peak plasma concentration of 383 ± 102 ng ml^{-1} was reached 52 ± 40 min after diazepam 10 mg orally and a peak plasma concentration of 650 ± 104 ng ml^{-1} was obtained 6 ± 5 min after diazepam 10 mg i.v. Finally, our subjects served as their own control and were studied under the same circumstances with and without diazepam.

On the basis of this study and the cited data we conclude that diazepam has no important clinical effect on gastric emptying.

Consequently, diazepam *per se* does not prolong gastric emptying, and should not increase the likelihood of nausea, vomiting, or delay in the absorption of drugs or fluid, and so increase the risk of aspiration of gastric contents.

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PIRACETAM DOES NOT CHANGE THE ANAESTHETIC REQUIREMENT FOR HALOTHANE

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SUMMARY

MAC of halothane was determined in rats before and after the injection of piracetam 0.5 or 2.5 g kg^{-1}, or both. No consistent changes in MAC were found. We conclude that piracetam is unlikely to influence halothane requirement appreciably.

Piracetam is a drug with effects on the brain which have led two investigators to propose that it promotes recovery from the effects of general anaesthesia (Samoya de Lyon, 1977; Samoya de Lyon, 1978; Nootropil, 1980a). The mechanism by which recovery might be accelerated is unknown, although a more rapid elimination of barbiturate has been suggested (Macarone Palmieri, Mastronardi and Paggio, 1977). These facts suggest that the use of piracetam during anaesthesia (as has been proposed) may increase anaesthetic requirement and the following study was undertaken to test this hypothesis.

MATERIALS AND METHODS

Two groups of eight female Sprague–Dawley rats weighing approximately 200 g were placed in individual clear plastic tubes through which halothane was directed in an average flow of oxygen of 1.5 litre min^{-1} per tube. The rectal temperature of each rat was monitored with a thermistor probe and maintained between 36.5 and 38.5 °C by external cooling (ice applied to the tube) or heating (infra-red light). Halothane delivered to the tubes was analysed by infra-red analysis (Beckman LB2).

MAC was measured by a variation of the standard technique described by White, Johnston and Eger (1974). After establishing the temperature at the limits cited above, we delivered a concentration of halothane thought to abolish movement in all rats (usually an inspired concentration of 1.4–1.6%) for a minimum of 15 min. A tail clamp was applied and moved for 1 min (or less, if the rat moved). The concentration of halothane was then decreased in steps of 0.2% and equilibrium established by waiting at the new concentration for 15 min. The rats were stimulated and observed for movement. This process was continued until all the animals had shown first a negative, and then a positive, response. The halothane concentration was then increased in steps of 0.2% and the process repeated at successively higher concentrations until no rat moved in response to stimulation. The MAC for each animal was calculated as the average of the concentrations bracketing movement and non-movement.

In the first group of eight rats MAC was determined as described above. Piracetam 0.5 g kg^{-1} was injected i.p. and MAC redetermined. Later, piracetam 2.5 g kg^{-1} was injected i.p. and MAC determined again. Following the second injection of piracetam, the rats were allowed to rest for 100 min after which MAC was redetermined.

In the second group ($n = 8$) the rats were anaesthetized for 2 h before MAC was determined. MAC was determined a second time (a second set of duplicate values) then piracetam 2.5 g kg^{-1} was injected i.p. and MAC redetermined.

Differences within each group were compared using paired t tests. Differences between groups were compared with unpaired t tests. $P < 0.05$ was accepted as significant.

RESULTS

In the first group of rats, there was a significant decrease in the MAC ($P < 0.025$) after the

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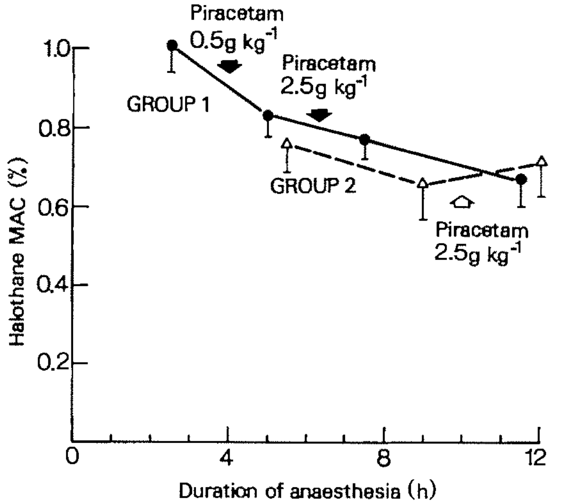

FIG. 1. The average MAC value appeared to decrease in group 1 rats after the injection of piracetam 0.5 g kg^{-1} ($P < 0.025$). However, the value after piracetam was not different from that obtained after the same duration of anaesthesia in the second group before the injection of piracetam. The injection of piracetam 2.5 g kg^{-1} produced no consistent change in MAC in either group. Values are mean ± SEM.

administration of piracetam 0.5 g kg^{-1}. However, the value after the administration of piracetam was not different from that obtained in the second group of rats after the same duration of halothane anaesthesia without the injection of piracetam (fig. 1). The injection of piracetam 2.5 g kg^{-1} did not produce a consistent change in MAC.

DISCUSSION

Our results do not support the hypothesis that piracetam increases anaesthetic requirement. The absence of an effect would not appear to be caused by the rapid elimination of piracetam from the brain. The drug has a longer half-life time in the brain than in the blood. In monkeys, 2–6 h after administration, piracetam is accumulated preferentially in the cerebral and cerebellar cortex (Ostrowski and Keil, 1978). This affinity is not species-dependent. A high affinity of the drug for the grey matter has been confirmed in the rat brain (Ostrowski, Keil and Schraven, 1975). In man, concentration of the drug in cerebrospinal fluid and blood suggest that piracetam readily enters the central nervous system (Calliauw and Marchau, 1975).

The absence of an appreciable effect of piracetam on MAC is unlikely to have resulted from our use of inspired as opposed to alveolar concentrations of halothane. The use of inspired concentrations as representative of alveolar concentrations might overestimate the alveolar concentrations. However, in rats the difference between inspired and alveolar halothane concentrations is less than 20% after 80 min of anaesthesia (White, Johnston and Eger, 1974), and since our studies continued for 700 min (fig. 1) our error should be well below 20%. Furthermore, any error should apply to both groups of rats. MAC in the untreated group (2) after 5–6 h of anaesthesia was no different from MAC in the treated group (1) at similar times.

If piracetam does affect anaesthetic requirement, the effect is small, and apparently clinically insignificant, at a dose several times greater than that used clinically (Nootropil, 1980b). It is possible that rats are less responsive than other species to the effects of piracetam. However, piracetam does appear to affect the capacity of rats to maintain ATP production in the brain during hypoxia (Nickolson and Wolthuis, 1976).

Our results appear to contradict those of other studies that imply a stimulant effect of piracetam, for example, a more rapid awakening from anaesthesia (Nootropil, 1980). Certainly piracetam is not an antidote to the anaesthetic state produced by halothane.

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ANAESTHESIA AND PROGRESSIVE MUSCULAR DYSTROPHY

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SUMMARY

The presentation and features of Duchenne's progressive muscular dystrophy (Duchenne's PMD) are described and the increased risks associated with anaesthesia are considered. Hazards associated with induction of anaesthesia and immediate postoperative recovery have been stressed in recent case reports, and these are summarized. Features of a hyperpyrexia-like response including cardiac arrest, increased serum creatine phosphokinase concentration, myoglobinuria and metabolic acidosis following suxamethonium or halothane, or both, have been described in patients with Duchenne's PMD. Subsequent in vitro *muscle tests have suggested that it is possible that a malignant hyperpyrexia response to general anaesthesia may occur. Six children known to have Duchenne's PMD who developed delayed respiratory insufficiency following anaesthesia and required controlled pulmonary ventilation are reported. In five of the children, cardiac arrest occurred despite apparently adequate respiratory support. Suxamethonium was common to the anaesthetic received by all six patients. In one of these patients subsequent anaesthetics, without suxamethonium, were uneventful and delayed muscle weakness did not occur.*

The Duchenne form is the most common and severe type of childhood progressive muscular dystrophy (PMD) with an incidence of approximately 30 per 100000 live births. The condition is caused by an x-linked recessive gene, although some of the affected boys are isolated cases with new genetic mutations—presumably occurring in the ovarian cells of the mother or maternal grandmother (Walton, 1983). Becker's muscular dystrophy, which is the other x-linked form, is milder and does not present as early nor run such a progressive course.

Duchenne's PMD usually becomes apparent between 2 and 6 years of age with the onset of a clumsy, waddling gait and frequent falling. Occasionally, affected patients do not develop the ability to walk. A characteristic feature is that of the child "climbing up his legs" on arising from the floor (Gower's sign). There is initial selective involvement of the muscles with, usually, the proximal muscle groups of the pelvis and the shoulders being affected first. The affected muscles may be large, as a result of infiltration by fatty tissue, but are nevertheless weak. This enlargement has led to the disorder being referred to as the pseudohypertrophic type.

Most boys with Duchenne's PMD show steady deterioration and are unable to walk by 8–11 years of age. Characteristically, by 13–14 yr they have difficulty propelling a wheelchair. Contractures are seen in these later stages, probably as a result of the unopposed action of antagonists of the dystrophic muscles. Progressive deformity occurs and kyphoscoliosis is common. Some patients become obese while others have a wasted appearance. Intellectual ability may be reduced. Skeletal atrophy can predispose to fractures of the shafts of the long bones.

Invariably there is myocardial involvement, but this is often masked by the incapacity caused by the skeletal myopathy. Heart and skeletal muscles are thought to share progressive muscular dystrophy abnormalities (Hunsaker et al., 1982). Electrocardiographic changes tend to be typical for Duchenne's PMD and are independent of the duration of the disease (Slucka, 1968). Characteristically these include a tall R wave in lead V_1, a deep Q wave in lateral precordial and limb leads, sinus tachycardia, and a shortened P–R interval (Perloff et al., 1967). The electrocardiographic

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pattern is considered typical enough to identify Duchenne's PMD from other myopathic disorders, even when clinical features are inconclusive (Perloff, DeLeon and O'Doherty, 1966). Obstructive cardiomyopathy with right ventricular hypertrophy can affect outflow, predisposing to right heart failure which may not be clinically apparent (Ellis, 1980).

Death usually occurs between 15 and 25 years of age. This may be attributed to pneumonia, aspiration pneumonitis, restrictive lung disease or cardiac failure.

The diagnosis of Duchenne's PMD is suggested by the typical clinical course and selective muscle involvement. Wasting may be obscured by fat, or there may be atypical muscle group involvement, necessitating the use of electromyography for confirmation of the myopathy. Serum CPK concentration is grossly increased from 30 to 300 times normal, and this occurs early in the disease. Muscle biopsies taken early in the course of the disorder show necrosis and phagocytosis of fibres with abortive attempts at regenerative activity. The fibre size may vary and show central nucleation, while fat and connective tissue infiltrate the muscle in later stages (Walton, 1983).

Anaesthetic considerations

Duchenne's PMD is a disorder which affects not only striated, but also smooth and cardiac muscle. Weakness of respiratory muscle and the decreased ability to cough can result in loss of respiratory reserve and accumulation of secretions which may lead to repeated chest infection. As the dystrophy progresses, the respiratory weakness becomes more important and the development of spinal deformities adds to the restrictive nature of pulmonary function. Consequently, pre- and post-operative physiotherapy, close observation in the recovery room, and additional oxygen therapy may be required. The intensity of management necessary will depend upon the degree of muscle disability.

Hypomotility of the gastrointestinal tract may lead to slower gastric emptying. Therefore at least 6 h starvation should be allowed before general anaesthesia in elective cases. If swallowing mechanisms and laryngeal reflexes are impaired, there will be a greater risk of aspiration than usual, particularly during the immediate postoperative period when the effects of anaesthesia are still present. Acute gastric dilatation occurring 48 h following surgery has been described by Wislicki (1962) in a patient with advanced Duchenne's PMD. She suggested that all affected patients requiring supine nursing should have a nasogastric tube passed as a prophylactic measure.

Myocardial involvement always occurs in patients with Duchenne's PMD. Tachycardia (Miller et al., 1978), ventricular fibrillation (Oka et al., 1982; Brownell et al., 1983) and cardiac arrest (Genever, 1971; Seay, Ziter and Thompson, 1978; Boltshauser et al., 1980; Linter et al., 1982) have been reported during the induction of anaesthesia. In all these patients in these case reports, Duchenne's PMD was unsuspected until further investigation was prompted by the occurrence of the cardiac manifestations. Ventricular fibrillation or cardiac arrest has also been described in patients known to have Duchenne's PMD, following a return of consciousness while the patient was still in the recovery room (Boba, 1970; Kelfer, Singer and Reynolds, 1983). The general anaesthetics which resulted in cardiac complications at induction all involved the use of suxamethonium. The majority used halothane as the induction agent, although one patient described by Seay, Ziter and Thompson (1978) had anaesthesia induced with cyclopropane. The patients described by Boba (1970) and Kelfer, Singer and Reynolds (1983) with postoperative complications, received only halothane for anaesthesia. Rhabdomyolysis as shown by myoglobinuria and markedly increased CPK concentrations was evident in the patients with cardiac problems following suxamethonium. This evidence of muscle breakdown was associated either with excess muscle rigidity after suxamethonium (Genever, 1971; Seay, Ziter and Thompson, 1978; Boltshauser et al., 1980; Linter et al., 1982; Brownell et al., 1983), or without rigidity (Miller et al., 1978; Seay, Ziter and Thompson, 1978; Oka et al., 1982). Brownell and colleagues (1983) and Kelfer, Singer and Reynolds (1983) obtained blood samples at the time of cardiac arrest and found marked hyperkalaemia. Metabolic acidosis was usually a feature (Miller et al., 1978; Boltshauser et al., 1980; Linter et al., 1982; Brownell et al., 1983; Kelfer, Singer and Reynolds, 1983), but was not always found (Oka et al., 1982).

Recently, it has been suggested that there may be an association between Duchenne's PMD and malignant hyperpyrexia (Oka et al., 1982; Brownell et al., 1983; Kelfer, Singer and Reynolds, 1983; Rosenberg and Heiman-Patterson, 1983). Malignant hyperpyrexia (MH) is characterized by: a progressive increase in body temperature; muscle contracture, usually after suxamethonium or in response to halothane or another inhalation anaesthetic vapour; myoglobinuria; hyperkalaemia; acidosis; cyanosis and tachycardia (Ellis, 1980). Episodes of MH may occur without significant fever or acidosis, but to support the diagnosis there must be evidence of increased aerobic or anaerobic metabolism (Gronert, 1980). Some features of MH were shown by many of the above case reports and *in vitro* tests for MH were carried out in some instances. Following cardiac arrest during anaesthesia, Oka and colleagues (1982) and Brownell and co-workers (1983) showed increased caffeine sensitivity of biopsied muscle fibres, from a 21-month-old boy and a 5-year-old boy, respectively. Rosenberg and Heiman-Patterson (1983) showed halothane sensitivity of biopsied muscle from a 4-year-old boy with Duchenne's PMD which they interpreted as being consistent with sensitivity to MH. Kelfer, Singer and Reynolds (1983), using a muscle biopsy from their patient, found decreases in the calcium uptake and adenosine triphosphatase activity of the sarcoplasmic reticulum. The results of this test, though, are not comparable to the usual halothane and caffeine contraction tests.

Some of the children described did not develop fever with the anaesthetic agents and the highest temperature recorded was 38.5 °C. Ellis (1980) stated that children with Duchenne's PMD may develop an increase in temperature which does not progress to malignant hyperpyrexia and can be managed by surface cooling. However, the *in vitro* muscle tests outlined above suggest that it is possible that an MH response to general anaesthesia may occur in Duchenne's PMD. Possibly these patients with their underlying cardiac muscle dysfunction are at greater risk from the increase in serum potassium concentration which occurs following suxamethonium administration. It may be that the high incidence of survival following cardiac arrest in these patients is the result of the transitory nature of the increase in serum potassium concentration (*cf.* burns patients).

Suxamethonium is known to release potassium from cells, increase serum CPK concentrations (Tammisto and Airaksinen, 1966) and cause myoglobinuria (MacLaren, 1968) in normal patients, including children. Halothane potentiates the enzyme-releasing effects of suxamethonium, but may also produce this result to a lesser degree when administered as a sole agent to normal patients (Lewandowski, 1982). The potassium- and enzyme-releasing effects are potentiated in patients with Duchenne's PMD and in patients with subclinical myopathy, as demonstrated by increased resting CPK and lactic dehydrogenase (LD) concentrations in serum (Lewandowski, 1981). Lewandowski (1982) described a boy with normal resting serum CPK concentration and increased serum LD concentrations who developed rhabdomyolysis, myoglobinuria, acidosis, tachycardia and hyperpyrexia following halothane and suxamethonium. Both the patient and a brother had strabismus and a cousin suffered from severe Duchenne's PMD. It was suggested that "the family is affected by subclinical dystrophy" and "may be prone to MH and/or rhabdomyolysis".

Recent experimental work suggests there is a spectrum of susceptibility to MH (Nelson, Flewellen and Gloyna, 1983). In addition, the presentation of MH is not always classical and confusion can easily develop as to whether this disorder is occurring. The diagnosis of MH susceptibility in patients with Duchenne's PMD should not be made without muscle biopsy and *in vitro* contracture studies, as the response to suxamethonium in particular, and inhalation agents, may be rapid breakdown of muscle giving a biochemical and clinical picture very similar to MH.

Although this discussion implies these patients are extremely vulnerable to anaesthesia, large series have been described in which no unexpected problems occur with anaesthesia provided the general state of fitness is reasonable (Cobham and Davis, 1964; Richards, 1972; Morris, personal communication (1984)). A variety of anaesthetic techniques was utilized in these patients, including the use of suxamethonium in some.

Delayed effects of general anaesthesia

In addition to the side effects during or immediately after general anaesthesia, instances of delayed muscle weakness leading to respiratory failure have been described (Watters, Karpati and Kaplan, 1977; Bush, 1979; Linter et al., 1982). There follows a more complete description of the patients previously referred to by Bush (1983). All these patients were known to be severely affected with Duchenne's PMD before anaesthesia.

Patient 1. Diagnosed as Duchenne's PMD aged 7 yr. At 9 yr he was admitted for left plantar fasciotomy and wedge removal from the lateral side of the left os calcis under general anaesthesia.

Thiopentone, suxamethonium, halothane, nitrous oxide and oxygen were administered, and endotracheal intubation performed. Uneventful anaesthesia and recovery occurred. On the 2nd day after operation, inadequate cough and the presence of secretions in his airway were noted. The following day there was no improvement despite conventional treatment. On the 4th day after operation, sudden cardiorespiratory collapse occurred. The patient was resuscitated, requiring tracheal intubation to allow suction and assisted ventilation. Tracheotomy was advised, but on induction of anaesthesia sudden cardiac arrest occurred. On this occasion there was no response to resuscitative efforts.

Patient 2. Diagnosed as Duchenne's PMD aged 9 yr. At 10 yr he was admitted for right plantar fasciotomy. Uneventful recovery from operation followed, but 9 months later he was described as having great difficulty in walking. When aged 13 yr he was admitted for dental treatment under general anaesthesia which consisted of thiopentone, suxamethonium, halothane, nitrous oxide and oxygen, and endotracheal intubation. After good recovery from anaesthesia he was discharged from hospital. However, readmission was required because of the onset of swallowing difficulties on the 2nd day after operation. The next day he developed a weak cough and tachypnoea. On the 4th day after operation, cardiorespiratory collapse occurred, requiring endotracheal intubation and controlled ventilation. Tracheotomy was performed on the same day. The following day sudden cardiac arrest occurred with resuscitative attempts being unsuccessful.

Patient 3. Admitted for dental treatment as a day case aged 14 yr. He had previously been diagnosed as having Duchenne's PMD. Thiopentone, suxamethonium, nitrous oxide and oxygen and possibly halothane were administered. Attempts at intubation were unsuccessful. He was discharged home later the same day. Admission was required again the next day because of difficulty in swallowing and breathing. He suffered a cardiac arrest from which he could not be resuscitated.

Patient 4. Diagnosed as Duchenne's PMD by muscle biopsy aged 6 yr. When aged 14 yr he was admitted for drainage of dental abscess. Before operation he was completely bedridden and unable to feed himself, but his chest movement was good and his lungs clear to auscultation. General anaesthesia consisted of methohexitone, suxamethonium, nitrous oxide and oxygen, halothane, nasotracheal intubation and spontaneous respiration. Following good immediate recovery from anaesthesia he developed respiratory insufficiency 9 h later. The trachea was intubated, 100% oxygen administered and artificial ventilation instituted. However, cardiac arrest supervened which failed to respond to treatment. Postmortem showed typical evidence of Duchenne's PMD.

Patient 5. This patient had spina bifida and Duchenne's PMD. An early operation closed the spina bifida and calipers allowed walking until aged 12 yr. When aged 17 yr he was admitted for dental treatment under general anaesthesia. Marked weakness of arms, chewing and swallowing was noted. Anaesthesia consisted of thiopentone, suxamethonium, nitrous oxide in oxygen and halothane. The trachea was intubated. Initially, he recovered well from anaesthesia, but 5 h later, developed difficulty in breathing with retention of secretions. The trachea was re-intubated, the secretions were removed, and with the onset of satisfactory spontaneous respiration the endotracheal tube was removed. Further respiratory difficulties developed 12 h into the postoperative period and intubation was required again. Mechanical ventilation, utilizing a trigger mechanism, was commenced. At 24 h into the postoperative period, he was breathing spontaneously for brief periods. After 6 days tracheotomy was performed and artificial ventilation continued. On the 12th day after operation there was a sudden deterioration of the cardiovascular system with eventual cardiac arrest.

Patient 6. Diagnosed as Duchenne's PMD by muscle biopsy under general anaesthesia aged 7 yr. He was dependent on a wheelchair 2 yr later. When aged 13 yr the patient was admitted for bilateral elongation of tendoachilles for equinus deformity of feet. General anaesthesia consisted of methohexitone, suxamethonium, nitrous oxide in oxygen and halothane. Endotracheal intubation was performed. Twenty-four hours after recovery from anaesthesia he developed difficulty in swallowing, requiring frequent pharyngeal aspiration. The weakness showed progressive deterioration so that, 3 h later, he was in extremis. Tracheal intubation was performed and artificial ventilation commenced. By the 3rd day after operation he was maintaining satisfactory spontaneous respiratory effort with a tidal volume of 250 ml. The trachea was extubated but required re-intubation, and the re-introduction of mechanical ventilation, 2 h later. On the 4th day after operation collapse of the right lung occurred but the patient was able to trigger the ventilator. Tracheotomy was performed under fentanyl and diazepam anaesthesia on the 5th postoperative day. By the 10th postoperative day he could tolerate 15 min per hour off the ventilator. Two days later he could manage without ventilatory support and the tracheostomy tube was removed on the 23rd day. Three weeks later he was noted to have a cough, stridor, and was described as "chesty". X-ray showed tracheal stenosis and he was readmitted for tracheal inspection and dilatation of the stricture under general anaesthesia.

Subsequently, over the next 4 months tracheal dilatation was required on five occasions and anaesthetic agents used included thiopentone, diazepam, fentanyl, nitrous oxide and halothane. Excellent recovery occurred from all anaesthetics without subsequent ventilatory embarrassment.

These six patients with Duchenne's PMD all had uneventful anaesthesia with postoperative muscle recovery to the level present in the preoperative period. However, delayed respiratory insufficiency developed 5–36 h following anaesthesia. Of the five patients who subsequently received apparently adequate pulmonary ventilation, four suffered a fatal cardiac arrest which may reflect the underlying cardiac myopathy. All six patients received suxamethonium at induction of anaesthesia. Patient 6, who was the only survivor of this delayed respiratory insufficiency, subsequently had anaesthesia on several occasions without suxamethonium, and no problems were encountered. The explanation for the onset of severe muscle weakness after a period of good recovery from anaesthesia must be speculative and further investigation of muscle function during such an episode is needed before any definitive conclusion can be drawn.

All these patients showed severe Duchenne's PMD, and perhaps this complication will be seen only at such a stage. This suggestion would be compatible with the experience of others who have not found difficulty with anaesthesia in patients with Duchenne's PMD. However, in view of the above case reports, extreme care should obviously be exercised for longer than is usual in the postoperative period. The delayed development of pulmonary insufficiency is a most unusual clinical feature, and this has drawn our attention to the problems of anaesthesia in Duchenne's PMD.

CONCLUSIONS

(a) Suxamethonium should be avoided in patients known to have Duchenne's PMD. Myocardial complications may follow suxamethonium during induction of anaesthesia. Suxamethonium was the common agent in the patients who developed delayed respiratory insufficiency after full recovery from anaesthesia. Patient 6 was managed uneventfully when suxamethonium was not used.

(b) Any untoward myocardial reaction in boys during induction of anaesthesia should alert the anaesthetist to exclude Duchenne's PMD.

(c) Recent case reports in the literature suggest that some patients with Duchenne's PMD are at risk of developing malignant hyperpyrexia.

(d) Precautions with patients with Duchenne's PMD should include temperature and electrocardiographic monitoring throughout anaesthesia. Dantrolene should be available in theatre and readily used if events consistent with a malignant hyperpyrexial response to anaesthesia occur.

(e) Where possible, local anaesthesia should be used to provide surgical analgesia.

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ANAESTHETIC PROBLEMS IN MYOTONIC DYSTROPHY

A Case Report and Review of the Aberdeen Experience Comprising 48 General Anaesthetics in a Further 16 Patients

L. M. ALDRIDGE

Myotonic dystrophy (dystrophia myotonica) is an autosomal dominant disease. It exhibits almost complete penetration but great variability of expression within affected families and notably between generations. It is the commonest dystrophy of adult life. Precise figures are few and those available are likely to be underestimates, as many cases fail to come to medical attention or are misdiagnosed. The figures from a number of centres indicate the prevalence of disease to be 2.4–5.5 per 100000 of the population. Only Duchenne dystrophy has a higher incidence at birth, although its prevalance is reduced by early mortality (Harper, 1979). While the muscles are affected primarily, myotonic dystrophy is a multi-system disease. The diagnosis may not be made until late in the disease and the presentation can therefore vary widely. Muscle pathophysiology consists of myopathy, myotonia or both. The histology of affected muscles is characteristic, with Type I fibre atrophy and Type II fibre hypertrophy being early features (Buxton, 1980; Anderson, 1985).

Typically, the patient has early facial weakness (expressionless face), wasting and weakness of the sternomastoids, ptosis, dysarthria, progressive distal muscle weakness and wasting (proximal involvement predominates in most myopathies) with myotonia or inability to relax the grip. Other features found to a variable degree are frontal balding, cataract, testicular atrophy, low IQ and ECG conduction defects. Mild disease presenting later in life may be associated with few symptoms and show few of the distinguishing signs.

SUMMARY

A previously undiagnosed case of myotonic dystrophy presenting with apnoea of 2.5 h duration following thiopentone is described. A review of the anaesthetic outcome from 49 operations in 17 patients with myotonic dystrophy in the Aberdeen area is presented. The type of operation and intra- and postoperative problems are analysed. The results reveal a 52% complication rate in previously diagnosed cases and a 35% complication rate in undiagnosed cases. In the series, 29% of the anaesthetics were administered to symptomatic patients before formal diagnosis. To avoid potential hazards it behoves the anaesthetist to remain alert to the possibility of the undiagnosed disease. The symptomatology and associated findings of the 17 patients at initial diagnosis are presented. The literature has been reviewed and anaesthetic implications noted.

CASE REPORT

In November 1983 a 48-yr-old woman with menorrhagia and an iron deficiency anaemia (haemoglobin concentration 9.6 g dl^{-1}) presented for dilatation and curettage (D&C). Despite there being "no medical history of note", perusal of notes established that in 1966 she had complained of stiffness and pain in arms and legs. No significant abnormality was detected and it was suggested that her symptoms were stress-induced, relating to a 20-week stillbirth delivered a few months previously. In 1968 a discrepancy was noted in the size of her calves; this was thought to have arisen from a previous subacute infection with poliomyelitis. In 1975 she experienced

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increasing pain in her back and legs. Sciatica was postulated and a brace supplied. In 1979 she was noted to have increased right leg pain, wasting and power loss.

In addition, there was a history of seven general anaesthetics during the years 1956–1966; six of those were for EUA and D&C arising in connection with investigations of infertility and spontaneous abortions. The seventh was for the insertion of Shirodkar suture. In June 1970 she was delivered at 35/40 weeks of a healthy male child.

On preoperative examination in 1983 the patient complained of tiredness, and of dyspnoea after one flight of stairs. This appeared unremarkable in an obese (weight 65 kg, height 1.52 m), anaemic 48-yr-old woman who was an occasional light smoker. The patient's arms and legs were disproportionally thin in relation to the obesity of her trunk, giving the impression of a Cushingoid appearance. Enquiry established the absence of any previous steroid therapy. It was only at the time of anaesthetic, following induction, that the small muscle wasting of her hands and feet became apparent.

General anaesthetic

Following premedication with lorazepam 3 mg by mouth, anaesthesia was induced with thiopentone 350 mg and nitrous oxide and halothane in oxygen were administered via a face mask. Spontaneous ventilation was inadequate and was accompanied by abdominal movements suggestive of respiratory obstruction. A Guedel airway was inserted without any noticeable improvement.

Difficulty was experienced in ventilating the lungs adequately via the face mask and the Magill breathing system, resulting in the development of cyanosis and an increasing level of consciousness manifested by the patient attempting to speak. Increasing $F\text{I}_{\text{O}_2}$ to 50% effected little change and the trachea was readily intubated with an 8-mm cuffed oral tracheal tube following a further thiopentone 150 mg. Suxamethonium was avoided, as the severity of the respiratory depression in conjunction with her clinically apparent distal muscle wasting suggested the presence of neuromuscular disease. Following intubation, her lungs could be ventilated easily without evidence of obvious obstruction or bronchospasm. Her colour improved immediately, and she was maintained throughout the procedure on 66% nitrous oxide and 0.5% halothane in oxygen. Following termination of nitrous oxide and halothane, the patient failed to sustain adequate spontaneous ventilation, despite continued vigorous abdominal movements.

Several attempts were made to wean the patient from the ventilator, but on each occasion cyanosis developed as the result of an inadequate tidal volume of 50–75 ml (Wright respirometer). One-and-a-half hours after the induction with thiopentone she remained apnoeic and was transferred to the recovery ward, where ventilation with nitrous oxide and oxygen was continued via a Manley ventilator. Doxapram was given, with marginally beneficial effect. The tidal volumes increased gradually; eventually sustained spontaneous ventilation was evident, some 2.5 h after the administration of thiopentone.

The patient was transferred to the ITU where improvement continued and by 6.30 p.m. (4.5 h after thiopentone) on $F\text{I}_{\text{O}_2}$ of 50% she achieved $P\text{O}_2$ 12.78 kPa, $P\text{CO}_2$ 5.64 kPa and pH 7.33. The trachea was extubated and the patient observed overnight. A neurological opinion was sought and the presumptive diagnosis of myotonic dystrophy was confirmed. Subsequent pulmonary function tests demonstrated a severe restrictive ventilatory defect. ECG was unremarkable.

RETROSPECTIVE SURVEY OF THE ABERDEEN ANAESTHETIC EXPERIENCE IN MYOTONIC DYSTROPHY

A search of the literature was prompted by this presentation of apnoea in an undiagnosed myotonic not possessing any features of the commonly quoted triad of frontal balding, testicular atrophy and cataract. A paucity of information exists on the hazards arising from anaesthesia in symptomatic myotonics at the prediagnosis stage; moreover, there has been no comprehensive and systematic review of the risks of anaesthesia in myotonic dystrophy since the only substantial series (Kaufman, 1960) recorded the hazards in the established disease.

In addition to reviewing, collating and summarizing the pertinent literature, the opportunity was taken to review the local experience. The Aberdeen area is well suited for epidemiological studies. The teaching hospital complex possesses a single hospital record system which is of considerable assistance in long-term clinical surveys. Records of the period 1969–1984 were searched and those of inpatients with muscular

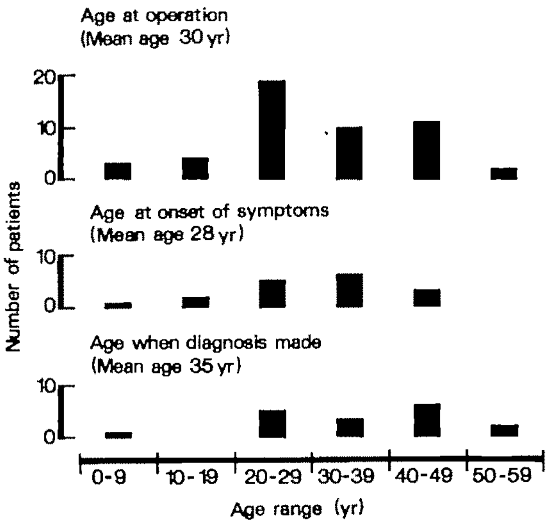

FIG. 1. Ages of the 17 patients (Aberdeen series) at onset of symptoms, at time of diagnosis and at time of operation.

disease extracted; 154 case records were examined and 38 instances of myotonic dystrophy identified. Seventeen of these patients (nine males) had received one or more general anaesthetic(s) with a total of 49 anaesthetic records being traced; of these 14 were in respect of operations before 1969. At the time of the study all the patients had been assessed and an unequivocal diagnosis of myotonic dystrophy made by a consultant neurologist.

Of the 49 operations, 17 were on the nine males and 32 on the eight females (two patients had each required eight operations).

The age at operation (fig. 1) in males was in the range 3–58 yr with a mean of 32.1 yr, and in females 5–49 yr with a mean of 29.7 yr. The mean age at first onset of symptoms was 28.6 yr in both male and female. The age range at the time of diagnosis was 6–52 yr for males (mean 34.8 yr) and 21–48 yr for females (mean 36.3 yr).

Particulars were extracted from each patient's record of the symptoms and signs present at the time of diagnosis (fig. 2), and of the duration of symptoms antedating diagnosis. The disease process was staged at the time of general anaesthetic(s). The anaesthesia and postoperative events were tabulated in detail.

Sex ratio ("1" in figure 2). In accord with all published series, the sex incidence was equal.

Family history (2). Batten and Gibb (1909) reported an affected brother and sister. The disease has, from subsequent series, been established to conform to the criteria for autosomal dominant inheritance with a very low proportion of new mutations (Klein, 1958).

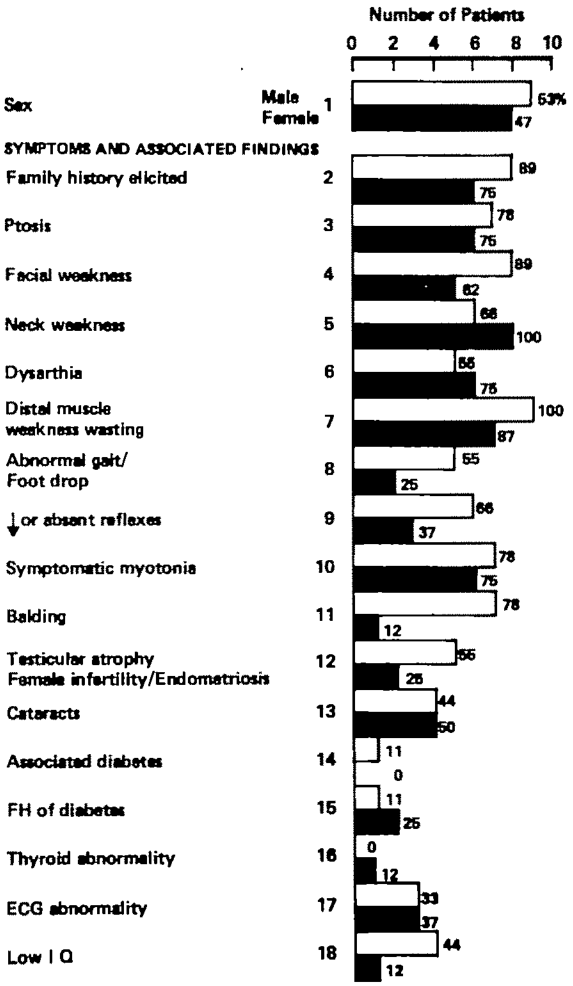

FIG. 2. Sex distribution, symptoms and associated findings in the 17 patients at the time of diagnosis.

Muscle weakness (*3–9*). The predominant initial signs arise from ptosis and facial muscle weakness, but the insidious onset is such that by the time of diagnosis the patient may demonstrate a wide variety of symptoms and signs. Cranial and distal muscle weakness predominate.

Myotonia (*10*). Although myotonia is present in most symptomatic patients, it may be concealed on handshaking by employing a variety of trick manoeuvres (Harper, 1979). The myotonia may also be reduced by warmth and repetitive movement.

Balding (*11*). Balding was present in 78% of males (mean age 35 yr) and one female (age 48 yr). The rarity of balding even in affected women and its common occurrence in non-affected men make it a poor clinical discriminant of the disease.

Testicular atrophy (*12*). The association of testicular atrophy with myotonic dystrophy has been known since 1909 (Steinert, 1909) and its prevalence has been recorded at 62.8% (Klein, 1958). If present, it is unlikely to be detected by the anaesthetist at preoperative assessment, and unless revealed on routine examination it is unlikely to alert attention to the undiagnosed case.

Cataract (*13*). Cataracts have long been recognized as a feature of myotonic dystrophy (Greenfield, 1911). In the early stages the typical multicoloured subcapsular lens opacities can only be identified by slit lamp examination. When mature, the cataract is indistinguishable from those arising from other causes.

Endocrine (*14–16*). The basis of the endocrine abnormalities recorded in myotonic dystrophy remains unexplained. Abnormal insulin responses to glucose load have been reported in myotonic patients without diabetes (Huff, Horton and Lebowitz, 1967) and the incidence of diabetes may be increased.

Thyroid colloid goitres have been reported (Benda et al., 1954). There was one case of colloid goitre in this series.

Cardiological (*17*). The incidence of ECG conduction abnormalities in myotonic dystrophy has been documented (Church, 1967). The commonest defect is first degree heart block, which affected one patient. A variety of rhythm disturbances have also been documented by Church and two patients in the series exhibited minor atrial arrhythmias.

Low IQ (*18*). Mental abnormalities have been observed in myotonic dystrophy. Although five patients were noted to have low IQ, a number of others were described as "apathetic". Klein (1958) has reported mental deficiency in 22.1% and apathy in 13.1%.

Despite the comparatively small numbers occasioned by the application of general anaesthesia as a selection criterion, the detailed analysis of the symptoms and associated findings at diagnosis reflect an acceptable comparison with the spectrum of disease reported in previously published series.

TABLE I. *Types of operation*

Gynaecological (*n* = 18)	D&C/EUA	13
	Laparoscopic sterilization	1
	Hysterectomy	1
	Salpingo-oophorectomy	1
	Cautery of cervix	1
	Shirodkar suture	1
	(13 between two patients)	
Genitourinary (*n* = 1)	Cystoscopy	1
Dental (*n* = 4)	Extraction/conservation	4
ENT (*n* = 4)	Tonsillectomy	2
	Adenoidectomy	1
	EUA hypopharynx	1
Orthopaedic (*n* = 6)	Open reduction fracture	3
	Screw removal	2
	Anterior spinal fusion	1
	(4 on one patient)	
General surgery (*n* = 9)	Cholecystectomy	3
	Thyroidectomy	1
	Appendicectomy	1
	Herniotomy	1
	Excision lipoma	1
	Varicose veins	1
	Lumbar sympathectomy	1
Eyes (*n* = 7)	Cataract	3
	Needling	3
	Retinal detachment	1
	(4 on one patient)	

Anaesthetics

Procedures for which the general anaesthetics were given are detailed in table I. All the orthopaedic operations were on males. Two of the three cholecystectomies were on males.

Table II abstracts details of the 49 general anaesthetics administered, detailing premedication and induction and use of neuromuscular blocking maintenance and reversal agents. The complication rate in diagnosed patients was 52% and in undiagnosed patients 35%. The latter has been subdivided between operations undertaken during the symptomatic and the asymptomatic stages of prediagnosis. The complications recorded are presented in table III.

Grading of Disease (*according to Gillam and colleagues* (*1964*))

Grade I = mild.

TABLE II. *Type of general anaesthetic and problems encountered.* ● *Grade III severity, remainder of patients Grade I and II.* ▲ *Diagnosis made following anaesthetic complications. Type of problem described by A-H. (see table III). Elsewhere in table: STP = Thiopentone; Mxt = methohexitone; γOH = gamma OH; N = nitrous oxide; P = methoxyflurane; E = enflurane; H = halothane; O = oxygen; Sux = suxamethonium; N-D = non-depolarizing muscle relaxant; A = atropine. Neo = neostigmine*

								Undiagnosed				
	Type of general anaesthetic					Diagnosis known		Symptomatic		Antedating symptoms		
Premed.	Induction	Relaxants	Maintenance	Reversal	Total no. of GA	No. of GA	Problems	No. of GA	Problems	No. of GA	Problems
—	STP		NOH		3	1		2	D		
Opiate	STP		NOH		12	1	A	2		9	
—	STP	Sux	NOH/P/NO		8			4	B+E▲	4	
Opiate	STP	Sux	NOH/NO		5	2	Fb●	2	G	1	
—	NOH		NOH		1	1					
—	NOH		NOH+ Extradural		1	1	Fd●				
Opiate	NOH		NOH		3	3	Fa				
—	Mxt		NOH		1	1					
Opiate	Mxt+NOH		NOH/P		2	2	Fa				
Opiate	Mxt	Sux	NOH/P		1			1			
Opiate	Althesin		NOP		1			1			
Opiate	γOH+Mxt				1	1					
Opiate	Etomidate		NO		1	1					
Opiate	STP	Sux N-D	NOH	A+Neo	2	1	C+Fa●	1	Fa		
Opiate	Althesin	Sux N-D	NOH	A+Neo	1	1	B+C				
Opiate	STP	N-D	NOH/NO	A+Neo	4	3	Fe Fa C	1	●Fd+Ha▲		
Opiate	Etomidate	N-D	NOE	A+Neo	1	1	Fc+Hb●				
Opiate	Althesin	N-D	NO+ Althesin infusion	A+Neo	1	1					
				Totals	49	21 52% Complication rate	11	14 35% Complication rate	5	14	0

TABLE III. *Types of complication*

During and immediately after operation		
A	Respiratory depression from opiate premed.	1
B	Rigidity/very difficult intubation after Sux.	2
C	Respiratory depression/incomplete reversal following neostigmine	3
D	Prolonged apnoea after STP (2.5 h)	1
E	Prolonged apnoea after STP and Sux (30 min; subsequent STP without respiratory depression)	1
	Total	8
After operation		
F	Chest infection	
	(a) Minor	5
	(b) With pleural effusion	1
	(c) Pneumonia	1
	(d) Pneumonia with profound respiratory depression and collapse occurring on 2nd day after op. (both had methadone 10 mg 2–3 h before collapse)	2
	(e) Mild chest infection preceding sudden death 30 h after operation	1
G	Transient generalized muscle weakness	1
H	Cardiovascular	
	(a) Myocardial infarction	1
	(b) First degree heart block	1
	Total	13

Grade II = moderately severe, but patient still able to undertake light work or domestic duties.

Grade III = patient severely incapacitated, unable to walk far and considered semi-invalid.

Grade IV = patient bedridden.

No Grade IV patients were identified in this series. Of the six operations recorded on Grade III patients, only one anaesthetic (which used opiate premedication, nitrous oxide, oxygen and halothane for induction, tracheal intubation and maintenance) was without complication. The complications attendant on the other five operations are indicated in table II. At the time of operation the remaining patients were asymptomatic or Grade I or II in severity.

DISCUSSION

In this series three of the 17 patients (17%) had cholelithiasis. A high incidence of gallstones is a feature of myotonic dystrophy, with an unusual male predominance reported by Robert and colleagues (1972).

Following cholecystectomy, postoperative morbidity and mortality related to respiratory problems is well recognized, with tracheotomy or postoperative ventilation, or both, often being required (Talmage and McKechnie, 1959; Kaufman, 1960; Tsueda, Shibutani and Lefkowitz, 1975; Meyers and Barash, 1976; Buzello, Krieg and Schlickewei, 1982).

Intraoperative/immediate postoperative complications

The complications occurring during and immediately after operation (table III) were all drug-related: the later postoperative complications tended to reflect the severity of disease.

It is helpful to consider those predictable adverse drug reactions which were related to dosage/disease process, separately from those which were idiosyncratic and occurred unpredictably in a minority of patients (Rawlings and Thompson, 1978).

Thiopentone. Respiratory depression occurred in two patients following the induction of anaesthesia with thiopentone. Both patients were undiagnosed at the time of operation. One patient (Grade I male) had also received suxamethonium following which intubation proved difficult by reason of rigidity. The patient's lungs were ventilated with nitrous oxide in oxygen for 30 min and thereafter recovery was uneventful. Thiopentone was used subsequently in reduced dose without any recorded complication. As the apnoea cannot be unequivocally related to the administration of thiopentone, this patient will not be discussed further.

The second patient is the subject of this case report. She had seven previous operations and on all occasions had received thiopentone (doses varying between 250 and 375 mg); adverse effects were not reported. Seventeen years had elapsed since the last of these operations, although at tha time, with hindsight, the patient appeared to have early symptoms of myotonia.

Prolonged apnoea immediately following induction has been reported in myotonic dystrophy (table IV). On all five occasions the patients had received an opiate premedication. In the Aberdeen series, severe respiratory depression occurred in one patient following opiate premedication, but responded to naloxone before subsequent uncomplicated induction with thiopentone.

In one instance of thiopentone apnoea (table IV) improvement followed nalorphine (Bourke and Zuck, 1957) but, while it is probable that opiates enhance respiratory depression, clearly thiopentone precipitates the apnoea. In the currently reported case, premedication was with lorazepam which, having a stimulatory effect on respiration

TABLE IV. *Previous reports of apnoea and respiratory depression following thiopentone*

	Apnoea with thiopentone		
Source	Dose of thiopentone (mg)	Duration apnoea (min)	Comments
Dundee (1952)	500	40	
	250	40	
Bourke and Zuck (1957)	500	120	+ Sux 50 mg
Hewer (1957)	100	40	
Lodge (1958)	100	40	
	Depression of respiration following thiopentone		
	Dose of thiopentone (mg)	Comments	
Dundee (1952)	50	No loss of consciousness	
Gillam and others (1964)	100	Increased narcosis in three out of six patients	
Mudge, Taylor and Vanderspek (1980)	100	Apnoeic but could breathe on command	

(Vickers, Schnieden and Wood-Smith, 1984), is unlikely to have contributed to the apnoea.

The mechanism for this apparent sensitivity to thiopentone remains in doubt. Dundee (1952) noted, in his first case, failure of carbon dioxide to stimulate respiration and an apparent return of consciousness before full respiratory volume was restored. In normal muscle the direct stimulant action demonstrated with relatively low concentrations of thiopentone has been shown to be masked with larger doses by the curare-like depression of myoneuronal transmission (Dundee and Wyant, 1974). On the basis of these observations he suggested the involvement of a peripheral mechanism entailing undue sensitivity of the affected musculature to thiopentone.

Depression of respiration with small doses of thiopentone has been recorded (table IV). Gillam and colleagues (1964) felt that the respiratory effect recorded in their series was associated with exaggerated narcosis. Hewer (1957) noted "deep unconsciousness" accompanying the thiopentone-induced apnoea.

In the Aberdeen series (table II) thiopentone was administered on 33 occasions (14 of which antedated the appearance of symptoms) without prolonged apnoea being noted. In Kaufman's 1960 series, 14 patients received thiopentone without adverse effect. Talmage and McKechnie (1959), Dalal and co-workers (1972), Ravin, Newmark and Saviello (1975) and Tsueda, Shibutani and Lefkowitz (1975) all recorded patients in whom thiopentone was given without adverse effect.

Although these reports suggest that myotonics do frequently show increased sensitivity to the respiratory depressant effects of thiopentone accompanied by an exaggeration of the normal response to narcosis, the prolonged apnoea attributable to thiopentone appears idiosyncratic. Such apnoea is not necessarily associated with CNS depression, and the previous uncomplicated use of thiopentone in the currently reported patient suggests it parallels the development of the disease. In this patient its persistence despite the initial return of consciousness was very similar to Dundee's experience and implies either, or in combination, a peripheral muscle effect or a remarkably selective depression of the respiratory centre.

It is pertinent that, during the period of apnoea, regular thoraco-abdominal movements were present, with a particularly vigorous abdominal component. The abdominal musculature maintains the intraabdominal pressure, upon which the efficiency of the diaphragm as a muscle of inspiration relies (Grimby, Goldman and Mead, 1976). It may also act as an accessory muscle of inspiration and expiration. The manner in which these movements are co-ordinated with the intercostal/accessory muscles is uncertain (Derenne, Macklem and Roussos, 1978a), but appears to require both input from the respiratory centre and integration at spinal level (Mitchell and Berger, 1975).

Thus, the continued thoraco-abdominal movements, despite their ineffectiveness, suggest functioning respiratory drive. This respiratory effort persisted throughout ventilation. It is unknown whether impairment of the afferent input from the abnormal muscle spindles in myotonic dystrophy (Stranock and Newsom Davis, 1978) has any significant effect on the control of respiratory rhythm, the generation of which has been comprehensively reviewed by Derenne, Macklem and Roussos (1978b). However, the failure of ventilation to inhibit respiratory effort is commonly observed in non-paralysed patients, suggesting that afferent input from lungs and chest wall is of limited importance in the control of human respiration (Widdicombe, 1961; Phillipson, 1978).

Diagnostic clinical patterns of thoraco-abdominal movement are well recognized (Goldman, 1982). Active inward (paradoxical) movement of the abdomen in inspiration occurs in obstructive airways disease and respiratory muscle fatigue arising from either central or peripheral causes (Ashutosh et al., 1975; Macklem, 1980). Myotonia of the intercostal muscles has been recorded (Benaim and Worster-Drought, 1954).

Passive abdominal movements may occur across a paralysed diaphragm (Macklem, 1980) and have been observed in quadriplegics with upper cervical lesions (Sharp et al., 1977). Diaphragmatic paralysis is responsible for the "seesaw" respiration of Stage III Plane IV ether anaesthesia (Guedel, 1951). In myotonic dystrophy, muscle fatigue (Roussos and Macklem, 1977) and myotonia (Kilburn, Eagen and Heyman, 1959) have been shown to affect the diaphragm.

In this case the ineffective ventilation in the presence of an intact respiratory drive appears likely to have arisen primarily from muscle dysfunction and would appear to support Dundee's original postulation of an idiosyncratic peripheral effect of thiopentone.

Suxamethonium. Myotonic muscle displays increased sensitivity to suxamethonium (Orndahl and Stenberg, 1962). This may exacerbate the myotonia, causing respiratory muscle spasm and consequent anoxia.

In the Aberdeen series two symptomatic patients (16%) became rigid following suxamethonium, making intubation very difficult. One of these patients when asymptomatic some 8 years previously, had received suxamethonium in a similar dose without ill effect.

In the animal model, suxamethonium has been shown to increase serum potassium concentration (Paton, 1956). An increase in plasma potassium concentration has been demonstrated to bring about a parallel increase of muscular excitability in normal individuals. In patients with myotonic dystrophy it is associated with a bi-phasic phenomenon, the severity of the myotonia being initially decreased and then, at higher potassium concentrations, being markedly increased with the occurrence of spontaneous myotonic discharges (Durelli et al., 1982, 1983). It has been suggested that the increase in potassium concentration may form the basis of the adverse reaction to suxamethonium. Certainly, in conjunction with the bi-phasic phenomenon, it may explain the unpredictable nature of the response in myotonic dystrophy. However, if this explanation is valid, the reaction is not idiosyncratic and all myotonic patients must be considered at risk if there is a sufficiently marked increase in serum potassium concentration.

Thiel (1967), from an extensive review, concluded that depolarizing neuromuscular blocking drugs are best avoided, and that non-depolarizing drugs are not contraindicated provided there is an appreciation of the importance of adequate antagonism in the presence of muscular wasting and weakness.

Neostigmine. In three symptomatic patients (33%) in whom neostigmine was used to reverse non-depolarizing block, incomplete reversal was reported. The first patient was a 40-yr-old female (Grade II) who, after cataract surgery and following neostigmine 3.75 mg, complained of difficulty in breathing and required doxapram. Five months previously, at the time of cholecystectomy, this patient had received pyridostigmine 10 mg. Although postoperative breathing difficulties were not recorded, she did require a second dose of 4 mg.

The second patient was a 43-yr-old male (Grade III) who, following an appendicectomy, received initially neostigmine 5 mg and subsequently a further 2.5 mg. Difficulty in reversal was noted, reintubation of the trachea being required.

The third patient was a man of 40 yr with Grade II disease who, after anterior spinal fusion and reversal of tubocurarine with neostigmine 5 mg, was noted to have poor colour and breathing difficulties.

In 1937 Kennedy and Wolf reported increased myotonia following the use of neostigmine. Myotonic muscle has increased sensitivity to the stimulating effects of acetylcholine and choline (Orndahl, 1962). It has been demonstrated, in patients with normal muscles, that the neuromuscular paralysing action of neostigmine in the presence of a competitive blocking agent was increased when given in two sequential doses of 2.5 mg compared with a single dose of 5 mg. These findings indicate that, despite initial reversal with neostigmine, subsequent doses may, by acting on normal unblocked muscle, produce acetylcholine-induced depolarization blockade. It is postulated that apparent instances of inadequate reversal may have been attributable to overdosage with neostigmine (Payne, Hughes and Al Azawi, 1980).

A patient with myotonic dystrophy has been reported in whom attempts to antagonize residual non-depolarizing blockade with neostigmine were only partially effective and a further dose produced long-lasting muscular weakness which, on train-of-four response, resembled depolarization blockade. The precise mechanism remains unclear, but did not appear to be simply related to excess acetylcholine at the motor end-plate. The authors concluded that it was not possible to predict the type and degree of response to neostigmine. It was suggested, furthermore, that any anticholinesterase agent may be suspect and concern was expressed over the use of neuromuscular blocking drugs. If the use of such drugs is essential, the authors suggested that the shorter acting agents be utilized and any residual curarization dealt with by mechanical ventilation (Buzello, Krieg and Schlickewei, 1982).

Althesin. In one patient in the present series an Althesin infusion was utilized (male age 27 yr with Grade II disease) without complication. Suppan (1975) and subsequently Muller and Suppan (1977) reported the efficacy of an Althesin infusion plus pancuronium where either atrophy or myotonia was the major feature. Yee, Milliss and Lah (1981) have recorded an uneventful outcome using an infusion of Althesin.

Halothane. It has been postulated that the use of halothane may be potentially disadvantageous, in that myotonia could be precipitated by postoperative shivering (Thiel, 1967). This has not been recorded in the present series.

Later postoperative complications

Chest infections. Chest infections arising from muscle weakness and possibly aspiration affected 20% of the patients. The incidence reflected the severity of the disease, no complications occurring in the undiagnosed antedating symptoms group, two (14%) in the symptomatic undiagnosed group and eight (38%) in the diagnosis-known group. Despite the expected increased numbers of cholecystectomies in the overall spectrum of operations performed (table I), the latter incidence is clearly of significance for this relatively young group of patients (fig. 1).

Direct involvement of pulmonary or bronchial tissue by the disease process has not been demonstrated, but indirect involvement is of considerable importance and the cause of significant morbidity and mortality. Weakness and myotonia in both pharnyx and oesophagus cause defective swallowing, giving rise to frequent tracheal aspiration and, in patients in whom there is also repiratory muscle weakness, resulting in pneumonic lung changes (Garrett et al., 1969).

Involvement of the diaphragm has been recorded at autopsy (Londrès, 1935). Radiological studies have shown that the diaphragmatic abnormality is caused not only by weakness and atrophy, but also by myotonia (Kilburn, Eagen and Heyman, 1959). Myotonia of the intercostal muscles has been recorded by Benaim and Worster-Drought (1954). Early respiratory muscle weakness is common and disproportionately greater than weakness elsewhere (Serisier, Mastaglia and Gibson, 1982). Kilburn and co-workers (1959), measuring minute ventilation, reported that patients affected with myotonic dystrophy showed decreased responsiveness to hypercapnia and suggested the possibility of central respiratory centre depression, although Gillam and colleagues (1964) were unable to confirm this observation. Carroll and associates (1977) showed that, in several mildly affected patients, the ventilatory response to hypoxia was uniformly reduced, but only two patients showed a reduced response to hypercapnia. It was postulated that brain stem neuroregulatory mechanisms were at fault.

The control and modulation of respiration in patients with myotonic dystrophy has been reassessed by Bégin and colleagues (1980), using mean inspiratory flow rate and occlusion pressure measurements which are less affected by the mechanics of breathing than the measurements of minute volume used by previous investigators. The responses of 12 myotonic patients and 12 control patients to selective stimulation of the chemical drive of breathing (using hypercapnia, isocarbic hypoxia and hyperoxia) were compared. In responding to hypercapnia, myotonic dystrophy patients had a normal occlusion pressure but reduced ventilatory output, composed of a smaller tidal volume with a higher respiratory frequency. The results of the hypoxia test demonstrated a significant increase in ventilatory output in both patients and controls, the only difference being the pattern of breathing, characterized by a small tidal volume and higher frequency in myotonic dystrophy patients. Again in the hyperoxia tests, no differences between patients and controls were apparent, indicating that both peripheral and central chemoreceptors are well preserved in myotonic dystrophy. The patients entering this study were moderately affected by the disease process and caution should be exercised in extrapolating the results to severe disease. However, it would appear that many of the observations recorded by previous investigators in Grade II patients may have reflected muscle dysfunction rather than the integrity of the respiratory centre. Bégin and colleagues (1982) subsequently investigated the ventilatory performance of a group of 10 patients with moderate disease. They demonstrated that the ventilatory output was altered predominantly by weakness and fatiguability of the respiratory muscles during higher ventilatory performance and by increased impedance of the respiratory system at lower degrees of ventilation.

Sudden death. It seems likely that sudden death, which is not uncommon in the disease, arises from cardiovascular causes. Asymptomatic ECG abnormalities are common and changes consistent with cardiac damage are shown in 60% of patients studied by vectorcardiography; cardiomyopathy has been identified in more than 50% of patients studied at postmortem (Fearrington, Gibson and Churchill, 1964). The 30-yr-old female in the Aberdeen series with Grade II disease, died 30 h after laparotomy for bilateral oophorectomy. A minor chest infection was reported after operation. This was her eighth general anaesthetic and her fourth since the diagnosis had been made 7 yr before death. Other problems recorded with previous anaesthetics were respiratory depression following opiate premedication, and on a separate occasion a minor chest infection. Autopsy revealed lung congestion without any obvious cardiac lesion, but unfortunately no preoperative ECG was available for examination. The patient had an affected brother who collapsed and died suddenly at the age of 29 yr.

CONCLUSION

The high incidence of cataract and gallbladder disease in myotonic dystrophy renders the patients as a group more liable to exposure to general anaesthesia. In the patients reviewed, in the literature and from the present series, it can be seen that many of the difficulties have arisen as a result of either the diagnosis of myotonic dystrophy not being made before operation or underestimating the hazards of respiratory insufficiency.

The case has been reported in detail to illustrate the difficulties attendant on making an early diagnosis in a disease with such insidious onset, and further amplification of the difficulties is not required.

In known patients local anaesthesia should be used if possible, especially in patients with Grade III or IV disease. Myotonic dystrophy is not an absolute contraindication to general anaesthesia, provided the risks are anticipated and steps taken to minimize the complications.

A suggested outline of an appropriate technique of general anaesthesia, based on this survey, is given below.

APPENDIX

IMPLICATIONS FOR ANAESTHETIC MANAGEMENT

Anaesthetic drugs

Thiopentone. Avoid or only minimal dose (not more than 100 mg); preferable to use gaseous induction or etomidate.

Suxamethonium. Avoid altogether; often jaw is weak and it is possible to intubate without neuromuscular blocker.

Non-depolarizing agents. Preferable to use new short acting agents such as atracurium or vecuronium.

Neostigmine. With care!; may be better to ventilate until residual curarization wears off.

Opiates. Restrict dose to avoid respiratory depression. Monitor the action of any respiratory depressant drugs carefully.

General management

Pre-operative assessment. ECG, pulmonary function tests and blood-gas tension.

During operation. Monitor ECG and arterial pressure; use a peripheral nerve stimulator to monitor neuromuscular blockade.

After operation. Early physiotherapy; monitor respiratory adequacy; assist ventilation early if inadequate. It may be prudent to leave the endotracheal tube *in situ* until maximal muscle power has been regained and the anaesthetic effects diminished.

Tracheotomy may be required to control secretions if cough reflex is reduced.

Treat infections vigorously.

Keep patient warm and calm, as cold and emotional excitement increase myotonia.

In patients in whom hypoxic drive accompanies chronic ventilatory failure, controlled oxygen therapy should be used.

Management of myotonia

Myotonia as a result of surgical stimulus is not abolished by spinal block or tubocurarine, but can be obtunded by injecting procaine to the muscles (Landau, 1952). Severe troublesome myotonia may be treated by quinine hydrochloride 300–600 mg i.v. (Kaufman, 1960).

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DYSTROPHIA MYOTONICA AND ATRACURIUM

A Case Report

P. NIGHTINGALE, T. E. J. HEALY AND K. McGUINNESS

SUMMARY

Atracurium was used to produce neuromuscular blockade in a patient with dystrophia myotonica. Operating conditions were excellent and myotonia was not seen. Sensitivity to atracurium was not seen and spontaneous recovery was not prolonged.

Dystrophia myotonica is the most serious and the most common of the myotonic syndromes, with a prevalence of 5 per 100000 (Gardner-Medwin, 1980). Inheritance is autosomal dominant. It is characterized by myotonia, especially when cold, and progressive muscular atrophy affecting predominantly the face, neck, pharynx and distal limbs. It is a systemic disease associated with cataracts, frontal balding, gonadal atrophy and cranio–facial abnormalities. Cardiac arrhythmias and cardiomyopathy are common (Cannon, 1962). Pulmonary reserve is often severely diminished and death is usually attributable to cardiorespiratory failure in middle age. Patients are often apathetic, hypersomnolent and of low intelligence. Other abnormalities include altered gut motility—especially difficulty with swallowing (Pierce, Creamer and MacDermot, 1965), various endocrinopathies and hypogammaglobulinaemia as a result of the excess catabolism of IgG (Walton and Gardner-Medwin, 1981).

Many of these abnormalities may be present before the onset of muscle symptoms and diagnosis (de Backer et al., 1976). Patients presenting with systemic manifestations requiring surgery are at particular risk (Kaufman, 1960). Patients with dystrophia myotonica may be sensitive to non-depolarizing neuromuscular blocking agents, and the use of an anticholinesterase drug to antagonize any residual blockade should be avoided (Mitchell, Ali and Savarese, 1978; Buzello, Krieg and Schlickewei, 1982).

Atracurium is a neuromuscular blocking agent with a rapid elimination half-life which may obviate the need for reversal of residual neuromuscular blockade at the end of surgery. It is characterized by cardiovascular stability at normal doses (Payne and Hughes, 1981). These properties suggest that atracurium could be a valuable agent for use in patients with dystrophia myotonica.

There are no reported cases of the use of atracurium in this disease and, hence, we felt that it would be instructive to detail the action of atracurium in such a patient.

CASE REPORT

A 21-year-old girl weighing 55 kg requested sterilization. Dystrophia myotonica had been diagnosed 3 years previously, at which time she was said to have had severe disease for her age. The patient was admitted for assessment 2 days before operation.

At interview she presented a typical picture of dystrophia myotonica with ptosis, facial weakness and slurred speech. She denied all symptoms of cardiorespiratory disease. There was some difficulty with swallowing, but no symptoms of regurgitation.

Past medical history included appendicectomy and a further laparotomy when aged 12 yr. Details

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of anaesthetics and postoperative course were not available. Three weeks previously the patient had been admitted with a severe attack of pelvic inflammatory disease requiring bed-rest and antibiotics.

The patient smoked occasionally, drank little alcohol and had no known allergies. Current drug therapy consisted of procainamide 250 mg 6-hourly on occasional days. Her severely affected younger sister had died in the postoperative period following an emergency laparotomy, only 2 weeks before this admission.

Examination revealed the typical features of dystrophia myotonica mentioned earlier. Of note was the weak distal musculature. Arterial pressure was 120/80 mmHg but heart rate was 100 beat min^{-1} and the pulse of poor volume. The peripheral circulation was poor. Auscultation of the chest showed generalized poor air entry, but no added sounds. The cough effort was noted to be weak.

The following special investigations were normal: full blood count, biochemical profile including liver enzymes, thyroid function tests, glucose tolerance test and blood-gas tensions breathing air. Chest x-ray, ECG, and echocardiogram were within normal limits. Abnormalities were found in serum creatine kinase (159 iu litre^{-1} (20–130)) and IgG concentrations (7 g litre^{-1} (8–16)).

Skull x-ray showed the typical small pituitary fossa and also bilateral subluxation of the temporo-mandibular joints. Diaphragmatic screening revealed inco-ordinate action during quiet breathing. Barium swallow revealed difficulty in initiation of swallowing and poor clearance of barium from the oesophagus, with absence of primary stripping waves. Audio EMG was diagnostic with the typical "dive-bomber" effect. Full scale IQ was 73. Pulmonary function tests are shown in table I. There was a 37% decrease in forced vital capacity (FVC) and a 31% decrease in forced expiratory volume in the first second (FEV$_1$). The FEV percentage (FEV$_1$/FVC) was 93%. These figures indicate a restrictive ventilatory defect with no evidence of airways obstruction. The patient was unable to perform estimations of residual volume (RV), alveolar volume (*V*A), specific airway conductance ($s.G_{aw}$) and transfer coefficient (*K*co).

TABLE I. *Preoperative measurements of pulmonary function.* (**Cotes*, 1979)

	Patient	Estimated
FEV$_1$ (litre)	2.2	3.2
FVC (litre)	2.36	3.75
FEV$_1$/FVC	93%	85%
Indirect maximum breathing capacity (litre min^{-1})	78	115

In view of the probability of a difficult laparoscopy as a result of adhesions and pelvic inflammatory disease the patient's request for general anaesthesia was accepted.

Anaesthesia

No premedication was given. On arrival in theatre the patient was anxious with tachycardia and cool moist palms. A cannula was placed in a vein on the dorsum of the hand. Gel pad electrodes were placed for the continuous monitoring of ECG, frontalis muscle EMG, modified EEG and neuromuscular transmission (NMT). An automatic arterial pressure recorder (Dinamap) was attached to the arm opposite the NMT electrodes.

After baseline measurements of arterial pressure and heart rate had been obtained, anaesthesia was induced with fentanyl 50 μg and thiopentone i.v. All drugs were flushed through with saline. Thiopentone 200 mg was given slowly until apnoea occurred. Ventilation was then controlled using a Magill attachment and face mask. Nitrous oxide 70% in oxygen was given whilst control measurements of NMT were made.

Neuromuscular transmission was monitored continuously using train-of-four stimulation. The ulnar nerve was stimulated at the wrist and the evoked compound muscle action potentials were detected over the adductor pollicis. Four supramaximal stimuli at a frequency of 2 Hz and pulse duration 0.1 ms were applied every 20 s. The evoked compound muscle action potentials were sensed and analysed automatically (Datex ABM: Anaesthesia and Brain Monitor). The ratios of the first twitch to the control twitch (T1:T0) and of the fourth twitch to the first twitch (T4:T1) were displayed graphically and digitally. A continuous printout was obtained using an Epsom dot matrix printer.

Atracurium 5 mg i.v. was given. After 5 min, pharyngeal secretions were suctioned, but intubation was not possible. This manoeuvre caused an increase in frontalis muscle activity. Enflurane was added to the inspired gases and a further 5 mg of atracurium given i.v. Further suctioning was necessary 3 min later and a similar increase in frontalis muscle activity was seen. The inspired concentration of enflurane was increased, fentanyl 50 µg and thiopentone 50 mg were given i.v., and intubation was accomplished with ease.

Pulmonary ventilation using a Brompton Manley ventilator (tidal volume 10 ml kg^{-1}) was adjusted to keep $P\text{E}'_{CO_2}$ between 4.8 and 5.2 kPa. Oesophageal temperature was maintained between 36.4 and 37 °C. At laparoscopy, dense adhesions made visualization of the pelvic organs impossible and laparotomy was necessary. Fentanyl 50 µg and thiopentone 50 mg were given i.v. when skin incision caused an increase in frontalis EMG activity. Further increments of atracurium 2 mg were given i.v. when T1 had recovered to 20% of control. No further increments of atracurium were given after the application of the Filshie clips and spontaneous recovery from neuromuscular blockade was allowed. Enflurane was discontinued when T1 had recovered to 25% of control. When recovery from neuromuscular blockade was deemed adequate, ventilation was discontinued and spontaneous respiration soon ensued. When $P\text{E}'_{CO_2}$ had stabilized at around 5.3 kPa, nitrous oxide was discontinued. Emergence was rapid, the patient lifting her head and attempting to remove the tracheal tube. Following extubation, the patient was transferred to the recovery room for observation. Shortly after transfer to the recovery room the patient was sitting up and vigorously refusing any oxygen therapy. Observations of arterial pressure, heart rate and respiratory rate remained stable and there was no clinical evidence of a change in muscle tone or power from pre-operative values.

Postoperative discomfort was treated with dihydrocodeine 25 mg i.m. Deep breathing and coughing were encouraged by nursing staff and physiotherapists. There were no postoperative respiratory problems and the patient was discharged on the 4th day after operation.

Figure 1 illustrates the course of events.

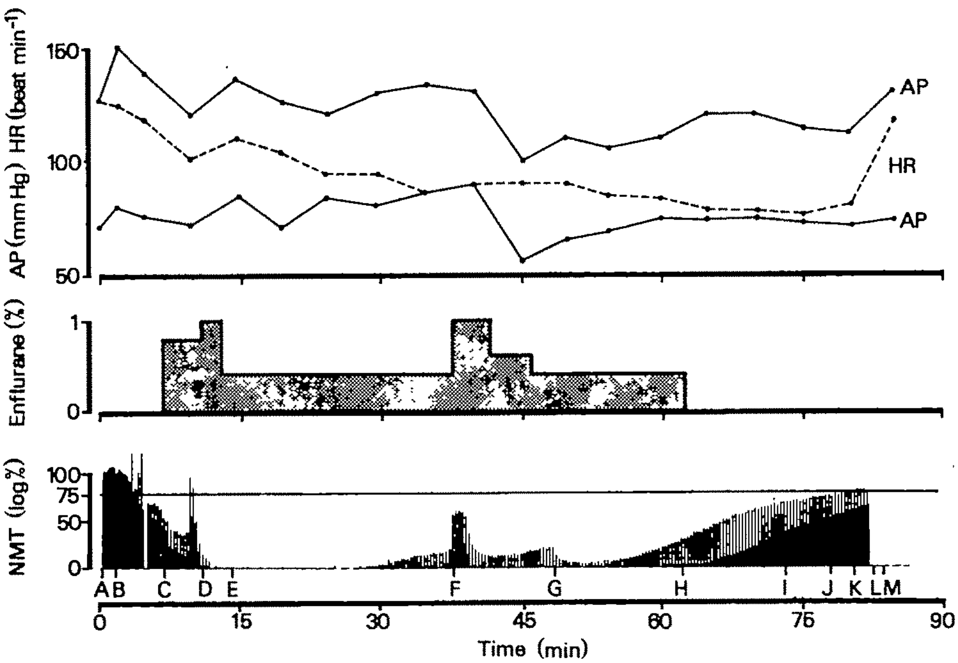

FIG. 1. The course of events: A = fentanyl 50 µg followed by thiopentone 200 mg; B = atracurium 5 mg; C = laryngoscopy for suction followed by atracurium 5 mg; D = intubation following laryngoscopy for suction, fentanyl 50 µg and thiopentone 50 mg (note NMT artefact associated with repositioning of the arms); E = start laparoscopy; F = skin incision, fentanyl 50 µg, thiopentone 50 mg and atracurium 2 mg; G = atracurium 2 mg; H = T4:T1 5%; enflurane discontinued; I = end of surgery; J = ventilation discontinued, onset of spontaneous respirations; K = T4:T1 75%; L = nitrous oxide discontinued; M = trachea extubated. NMT = neuromuscular transmission. AP: upper record = systolic; lower record = diastolic.

Neuromuscular transmission

Following each dose of atracurium, the "fade" pattern produced by non-depolarizing agents was seen. Five minutes following atracurium 5 mg, T1 was 50% and T4:T1 was 48%. Four minutes after a further 5 mg, T1 was 14%, T4:T1 was 0 and intubation was possible. Time to complete blockade of T1 was 10 min from the initial 5-mg dose. Two further increments of atracurium were necessary. The first was given 25 min after the second 5-mg dose. The second increment was given after a further 11 min. The time for T4:T1 to reach 75% of control after the last increment was 32 min. Spontaneous breathing returned when T4:T1 was 70% and extubation of the trachea was performed when T4:T1 was 78%.

Cardiovascular variables

The ECG showed sinus rhythm throughout. The preoperative tachycardia, presumably caused by marked anxiety, decreased rapidly following the induction of anaesthesia. There were increases in heart rate associated with intubation, skin incision and emergence. Arterial pressure was stable during surgery. An increase in arterial pressure was seen following induction and again at extubation, but not during intubation. The sharp decrease in arterial pressure shortly following skin incision was presumably the result of the rapid injection of fentanyl and thiopentone plus an increase in the inspired enflurane concentration.

DISCUSSION

Patients with dystrophia myotonica may be expected to be sensitive to non-depolarizing neuromuscular blocking drugs. Many reports, however, indicate a normal response (Dalal et al., 1972; Mitchell, Ali and Savarese, 1978). Certainly, these patients are sensitive to many of the drugs used in anaesthesia.

The rapid breakdown of atracurium by "Hofmann" elimination leads to a predictable recovery (Payne and Hughes, 1981), and was chosen with the hope of avoiding the use of neostigmine which may precipitate myotonia (Buzello, Krieg and Shlickewei, 1982).

Continuous neuromuscular monitoring enabled an accurate assessment of the degree of blockade and allowed observation of the rate of recovery. The type of monitoring enabled us to estimate that almost total recovery would have taken place by the end of surgery and we feel it is essential in the proper management of all cases of muscle dysfunction receiving neuromuscular blocking drugs. The ED_{95} for atracurium is approximately 0.2 mg kg^{-1}, depending upon the technique used (Basta et al., 1982; Goudsouzian et al., 1983; Black et al., 1985). The patient described here developed total block for 15 min following the initial doses of atracurium, which amounted to 0.18 mg kg^{-1}.

Enflurane is known to potentiate the action of neuromuscular blocking agents (Fogdall and Miller, 1975) and was indicated as an inhalation adjunct, so that smaller doses of a neuromuscular blocker could be used. Despite the use of enflurane, there was no obvious increased sensitivity to atracurium.

It was not possible to utilize T1 to monitor recovery, as a result of changes in the baseline—a problem well recognized with EMG recording. However, it is known that T1 is a poor indicator of recovery from non-depolarizing blockade and that recovery of T4:T1 is a more sensitive index. Recovery of T4:T1 to 75% reliably indicates recovery of T1 to control values (Ali et al., 1981, Calvey et al., 1983). The time for recovery of T4:T1 to 75% following the last increment of atracurium was 32 min, which is a normal rate of recovery.

It is our clinical impression that the incidence of postoperative shivering is low with enflurane. Shivering, especially when associated with a decrease in temperature, is known to induce myotonia (Ravin, Newmark and Saviello, 1975). Additionally, the use of an inhalation agent enables the dose of any narcotic to be kept to a minimum, thus decreasing the possibility of postoperative respiratory depression.

The case reported suggests that patients with dystrophia myotonia retain a normal sensitivity to atracurium. In view of its rapid elimination, obviating the need for an anticholinesterase drug, it is felt that atracurium should be considered when neuromuscular blockade is required for such patients. In addition, we believe that NMT monitoring is an integral part of the anaesthetic management of these patients, and full supportive facilities must be available.

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SCLERODERMA AND PREGNANCY

Anaesthetic Considerations

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SUMMARY

The case of a pregnant patient with diffuse scleroderma who died following Caesarean section under general anaesthesia is presented. The patient's postoperative course was complicated by pulmonary oedema and pulmonary hypertension, sepsis, thrombocytopenia and renal failure. Aspects of the disease which possess anaesthetic implications are reviewed.

Diffuse scleroderma (progressive systemic sclerosis) is a rheumatic disease characterized by inflammation, vascular sclerosis and fibrosis of the skin and viscera. The aetiology is uncertain and there is no effective form of therapy. The prognosis is poor and related to the extent of visceral, rather than cutaneous, involvement (Siegel, 1977). This disorder occasionally occurs in women of child-bearing age, who appear to maintain a normal fertility index (DeCarle, 1964). Consequently, diffuse scleroderma complicating pregnancy may occur.

The pregnant patient with simple acrosclerosis fares better than her counterpart with multisystem involvement. However, pregnancy has an unpredictable effect on the course of the disease (Slate and Graham, 1968). Indeed, morbidity and mortality are substantial among those mothers who develop concomitant hypertension (Fear, 1968; Karlen and Cook, 1974; Smith and Pinals, 1982). Therefore, the anaesthetist may have an integral role in the care of these high-risk parturients, especially if surgical delivery is planned. The recent report of Thompson and Conklin (1983) addresses the management of labour with regional anaesthesia. We offer the following case report to emphasize the considerations necessary for such patients if general anaesthesia is required.

CASE REPORT

The patient was a 24-year-old gravida 3, para 1, spontaneous abortion 1 with no living children. Diffuse scleroderma had been diagnosed by skin biopsy 18 months before admission. She had presented at the labour suite with premature rupture of membranes on the morning of admission. The patient had received no ante-natal care. However, from the history it appeared that the course of her pregnancy had been uncomplicated. The estimated gestational age of her fetus was 34 weeks. She was in active labour and was prepared for Caesarean section under general anaesthesia. (Her previous child had also been delivered by Caesarean section.)

Her history was unremarkable and she complained only of skin tightness in her limbs. Physical examination revealed normal vital signs and taut, shiny skin on the face, trunk and extremities. She could open her mouth about 4 cm and had full range of neck movements. A rapid sequence oral intubation was thought possible. Examination of the heart and lungs was normal. Serum electrolyte concentrations, urine analysis, blood count, prothrombin and partial thromboplastin times were within their normal ranges. A chest x-ray had been interpreted as normal.

Before the induction of general anaesthesia, the patient received 30 ml of sodium citrate 0.3 mol litre^{-1} by mouth and glycopyrrolate 0.4 mg via an existing cannula in a peripheral vein. She was positioned with left uterine displacement on the operating table. Following the inhalation of 100% oxygen for 5 min, a moderately difficult rapid sequence induction with endotracheal intubation was performed utilizing cricoid pressure, thiopentone 250 mg i.v. and suxamethonium 100 mg i.v. After the delivery of a vigorous male

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infant, anaesthesia was maintained with fentanyl, diazepam, and 50% nitrous oxide and 0.25% isoflurane in oxygen. At the end of surgery, the trachea was extubated when the patient was responsive and her protective airway reflexes had returned. She was taken to the recovery room and subsequently discharged in a stable condition.

Several hours later the patient was noted to be tachypnoeic. Scattered fine crepitations were present on auscultation of her lungs. A chest x-ray revealed bilateral perihilar infiltrates. Blood-gas determination showed Pa_{O_2} 7.3 kPa and a haemoglobin saturation of 86.2%. Volume overload was suspected and fluid was restricted, diuretics given and oxygen administered by face mask. Since these measures did not alleviate her respiratory distress, the patient was transferred to the surgical intensive care unit.

Upon arrival, the patient was sedated and a nasotracheal tube passed. The lungs were ventilated mechanically. Haemodynamic variables were obtained following placement of a pulmonary artery thermodilution catheter. These revealed a pulmonary artery pressure of 48/28 mm Hg, a pulmonary artery occlusion pressure of 22 mm Hg and a cardiac output of 7.5 litre min^{-1}. Her initial pulmonary and systemic vascular resistances were 138 dyne s^{-1} cm^{-5} and 1066 dyne s^{-1} cm^{-5}, respectively. It was also noted at this time that her urine output was diminishing progressively.

The patient's subsequent hospital course was complicated by worsening respiratory insufficiency, pulmonary hypertension refractory to vasodilator therapy, sepsis, thrombocytopenia and renal failure. Despite parenteral hyperalimentation, ventilatory support, daily haemodialysis and attempted reversal of her bleeding diathesis, the patient died 1 month post-partum. The cause of death was a massive upper gastrointestinal haemorrhage. Her infant was noted to have multiple congenital anomalies and died at 3 days of age from the complications of necrotizing enterocolitis. The family denied permission for autopsy in both instances.

DISCUSSION

The unfortunate outcome of this patient prompted an investigation of the implications which diffuse scleroderma holds for the obstetric anaesthetist. Literature describing the effect of scleroderma on the antepartum course of pregnancy and the management of labour with regional anaesthesia has been cited above. The body of knowledge specifically concerning the complications in these patients following Caesarean section is limited to case reports of pulmonary oedema (Hoffman and Diamond, 1967) and renal failure attributed to malignant hypertension (Ehrenfeld et al., 1977). In neither report was the type of anaesthesia mentioned. Therefore, the method of anaesthesia cannot be related to outcome and it is impossible to recommend a preferred anaesthestic technique for operative delivery.

In this patient a general anaesthetic, rather than a regional technique, was chosen for two reasons. First, scar formation is presumed to be abnormal in scleroderma. It was thought that general anaesthesia would offer greater haemodynamic control should massive haemorrhage occur in the event of rupture of the previous uterine incision. Second, reports exist which attest to the unpredictable spread and prolonged duration of local anaesthetics in such patients (Eisele and Reitan, 1971; Thompson and Conklin, 1983). With this in mind, there seemed to be a very real possibility of sudden respiratory insufficiency with loss of protective airway reflexes should total spinal or total extradural anaesthesia occur inadvertently. This consideration also argued for general anaesthesia to secure the airway initially under controlled conditions.

Although these are the considerations which related directly to the selection of anaesthestic technique, the underlying disease process affects organ systems other than those involved in reproduction. Thus, it would appear pertinent to review those abnormalities which may further influence the choice or conduct of anaesthesia in such patients.

Intravenous access is obviously impeded by dermal thickening. Raynaud's phenomenon may produce arterial vasospasm and inhibit peripheral perfusion. Musculoskeletal abnormalities such as flexion contractures of the extremities, as well as pre-existing avascular necrosis of the femoral head, have been described (Wilde, Mankin and Rodnan, 1970). Moreover, tightening of facial skin and mandibular resorption may irreversibly narrow the oral aperture (Ryatt, Hopper and Cotterill, 1982). Keratoconjunctivitis sicca exists in some patients and may predispose to corneal abrasions (Osial et al., 1983). Gastrointestinal involvement may produce incompetence of the lower oesophageal sphincter, as well as malabsorption of fat-soluble vitamins from the small bowel.

The kidneys, heart and lungs are major target organs in diffuse scleroderma. Unsuspected renal involvement is common (D'Angelo et al., 1969) and in the pregnant patient may produce the abrupt onset of overt kidney failure (Fear, 1968; Karlen and Cook, 1974). Myocardial dysfunction may occur as a result of sclerosis of the smaller coronary arteries and the conducting system (D'Angelo et al., 1969; James, 1974). Abnormalities of cardiac perfusion may be present, and appear to be attributable to a disturbance of the myocardial microcirculation (Follansbee et al., 1984). Finally, pulmonary fibrosis and arterial sclerosis are expected in far-advanced scleroderma. However, it is not widely appreciated that significant pulmonary hypertension may be present in an asymptomatic patient with a normal chest x-ray and only mild abnormalities of pulmonary function (Sackner et al., 1964; Ungerer et al., 1983).

With the above considerations in mind, we offer the following suggestions for management of such a patient under general anaesthesia. Positioning is best accomplished with gentle guidance, and the co-operation of the awake patient. A centrally-placed catheter may provide the most reliable i.v. access. Maintenance of a warm operating room environment and avoidance of peripheral i.a. cannulation may prevent the vasospasm of Raynaud's phenomenon. Care should be taken that the eyes remain protected at all times. If it appears that a rapid sequence induction will be technically difficult, an awake intubation, perhaps under endoscopic direction, may be advisable to guard against aspiration. Finally, it may be desirable to insert a pulmonary artery catheter before the induction of anaesthesia, especially if impaired renal function, pulmonary hypertension or cardiac dysfunction is suspected. With invasive monitoring, the haemodynamic effects of both peripartum volume shifts and anaesthetic agents, including nitrous oxide (Hilgenberg, McCammon and Stoelting, 1980; Schülte-Sässe, Hess and Tarnow, 1982), may be rapidly assessed. Moreover, the efficacy of any proposed therapy with pulmonary vasodilators, such as calcium antagonists (Rozkovec et al., 1983) or nitroglycerine (Pearl et al., 1983), may be readily determined.

To summarize, diffuse scleroderma is a disease of multiple organ system derangements, each of which has a specific implication for the conduct of general anaesthesia. The pregnant patient with scleroderma presents a special challenge in anaesthetic management because of her potential for precipitous cardiopulmonary and renal insufficiency. Moreover, should general anaesthesia be selected, an appreciation of the anaesthetic precautions necessary for the care of these patients may prevent serious perioperative complications.

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BOOK REVIEWS

Acute Pain. Edited by G. Smith and B. G. Covino. Published by The Butterworth Group. Pp. 283; indexed; illustrated. Price £32.50.

Whilst there are many texts covering chronic pain, this book is the only one that comprehensively covers acute pain in general and acute postoperative pain in particular.

The first chapters on the physiology and psychology of acute pain are a good introduction to the methods of acute pain relief which follow. These are covered in a logical manner and, despite the multi-authorship, there is a continuity of style which makes the whole book easy to read. "Measurement of Pain" and the "Neuroendocrinology of the Postoperative State" have their own chapters, but the effects of inadequate pain relief — sprinkled throughout several chapters — are difficult to find. Local anaesthetic techniques of acute pain control are extremely well covered. Analgesia for specific body areas is described in one chapter on somatic nerve blocks and is followed by a chapter on subarachnoid and extradural techniques and their effects.

Pharmacological methods of acute pain control spread across several chapters. The pharmacokinetics of the different agents and commonly-used routes of administration are presented clearly. Newer opioids are put in their place, in a chapter which includes a review of opioid receptor theory. The final chapter on non-pharmacological methods of pain relief completes an excellent book.

All anaesthetists will find this book useful and it will be an invaluable addition to any library. A service all anaesthetists interested in the relief of acute, severe pain can perform is to recommend this book to their medical and surgical colleagues.

Harry Owen

Clinical Anesthesiology. By B. R. Brown jr, C. D. Blitt and R. W. Vaughan. Published by the C. V. Mosby Company, St Louis, Toronto, Princeton. Pp. 401; indexed; illustrated. Price £27.

The introduction to this book states that it is designed for undergraduates to be read during their clinical clerkship in "anesthesiology." The authors have produced a very comprehensive and quite detailed account of clinical anaesthetic practice. There are chapters on pre-operative evaluation, pharmacology of anaesthetic drugs (including all the structural formulae), monitoring, induction of anaesthesia, the recovery period, regional anaesthesia etc., together with a chapter on subspecialties such as anaesthesia for paediatric and cardiac surgery as well as chapters on respiratory failure, and acute and chronic pain. The chapters are clearly divided into sections and the many sub-headings in the text make it an easy book to find one's way around.

In the opening pages there are a brief historical introduction, a definition of the specialty and emphasis of the point that, in circumstances where there is no medically trained "anesthesiologist," the surgeon is ultimately responsible for the "conduct of the anesthesia and for the actions of a nurse anesthetist." It is probably for this reason that the text contains detail which, for the British undergraduate, could be considered excessive.

The contents, as one would expect from these authors, are first class, although I do have certain reservations. The text provides quite detailed practical instructions on techniques such as passing a Swan–Ganz catheter and performing a sciatic nerve block. The section on anaesthesia for cardiac surgery is 10 pages long! While not being sufficiently detailed for the postgraduate, to burden an undergraduate with all the information that is given here seems unnecessary. In addition, the final chapter consists of several anecdotal blow-by-blow accounts of anaesthetic administration which, by the very nature of the speciality, must be idiosyncratic. The language is very American and one feels that the authors could have got their points over in slightly less than the 400 pages they have taken. Sentences such as "utilisation of these devices by medical and nursing staff necessitates a significant dedication to education" tend to grate on the English ear.

In short, this book provides an excellent introduction and overview of clinical anaesthetic practice but, in the U.K., would probably be more appropriate as an introductory text for the postgraduate than as an undergraduate textbook. At £27 a copy, it would probably be out of the financial reach of most undergraduates, anyway.

Iain T. Campbell

Intensive Care. Edited by G. Gerson. Published by William Heinemann Medical Books. Pp. 312. Price £12.50.

Dr Gerson states in his introduction that this book is intended as a practical guide for junior medical and nursing staff in intensive care.

It is a slim volume and, as it attempts to cover all areas of intensive care, excluding burns and postoperative management, in 300 small pages, it is very brief and at times rather dogmatic.

There are nine chapters, six of which cover the major organ systems and one each covering poisoning, shock and parenteral nutrition. They are generally well presented and clear, with the chapters on respiratory management and renal failure particularly good. However, I feel that where space is limited the devotion of one-fifth of the book to a chapter describing the management of myocardial infarction is unfortunate when only the scantiest information is provided on topics such as the control of infection in the I.C.U., the interpretation of the results of invasive haemodynamic monitoring, and the management of chest trauma.

The book can be recommended to a junior about to enter the Intensive Care Unit for the first time, but to one determined to make a career in anaesthesia a longer, more stimulating text would, in all probability, repay the additional expense.

Brian Gowan

Monitoring in Anaesthesia. Edited by Saidman and Smith. Published by Butterworths, Sevenoaks. Pp. 556; illustrated; indexed. Price £50.

The second edition of *Monitoring in Anaesthesia* updates the very successful first edition and includes new chapters on the EEG, Paediatric Monitoring and Computers. Twenty-one expert authors including one from the U.K. discuss monitoring of depth of anaesthesia, respiratory, cardiovascular and neurological function, body chemistry, neuromuscular blockade and occupational exposure. Monitoring in the recovery room and intensive care unit are also included; the final chapters deal with selection and maintenance of equipment, and future trends.

The importance of monitoring is highlighted in the Foreword. "A mishap is no longer accepted as an 'act of God' but is found to be a fault for which someone is held liable." This rather dogmatic U.S. consumer view should not distract us from aspirations to greater safety and near zero mortality.

Most chapters begin by explaining the underlying physiology of the system monitored and validate parameters actually measured. There is, in fact, far more basic physiology in both the chapters on monitoring of respiratory function and neuromuscular blockade, than on actual monitoring.

In the chapter on body chemistry measurement, good arguments are given for quality control in laboratories. Where details are given they are usually of considerable practical value, for example, seven times the volume of the catheter needs to be flushed before the critical sample is drawn (from indwelling lines).

Pleas for monitoring are a theme throughout the book. "In view of the possible mechanical mishaps which alter respiratory function this parameter should be monitored even prior to induction of anaesthesia." Continuous monitoring of oxygen delivery is advocated. It would seem that apnoea alarms are in greater use in the U.K. at present. There is logical progression from watching the reservoir bag to discussion of mass spectrometry.

The definition of monitoring does not appear until the fourth chapter, on Invasive Monitoring of the Circulation, which also discusses indications for monitoring. Non-invasive monitoring includes a long discussion of systolic time intervals in which LV$dP/dt$ is discussed without consideration of its limitations. Calculations of systolic time intervals seems so complex that one could be forgiven for preferring invasive techniques! The futuristic view is presented where M-mode echocardiography is used to measure cardiovascular responses to anaesthetic induction agents.

The chapter on monitoring the EEG and evoked potentials during anaesthesia contains rather an excess of technical detail and there is considerable overlap with the chapter on neurosurgical monitoring, which contains much valuable practical information. The sensitivity of techniques for detecting air embolus are usefully compared and intracranial pressure monitoring evaluated, whilst clinical neurological assessment is not underestimated.

The chapters on maternal–fetal monitoring and occupational exposure are very clear. Fetal heart rate monitoring in at-risk infants is one of the most potentially valuable continuous monitoring techniques available. Considerable controversy exists at present regarding cost effectiveness.

Special considerations in monitoring children during anaesthesia starts with "the experienced eye" and proceeds, totally unillustrated, to evaluate the significant variations in monitoring equipment and techniques in this age group. Monitoring occupational exposure draws on U.S. experience and recommendations and discusses the function of monitoring programmes and instruments for nitrous oxide analysis.

The chapter on monitoring in the recovery room and surgical intensive care unit contains an interesting discussion of classifying patients by risk group and the philosophy of monitoring so as to reduce overproduction of data. It also draws attention to monitoring the whole patient. There is a basic discussion of the working of computers and their application in charting control of anaesthesia, capnography and automatic arterial pressure devices. This chapter includes a useful glossary. The book ends with chapters on electrical safety, the very important topic of selection and maintenance of equipment and a look at future trends. It is suggested that the emphasis will change from acquisition of data to its analysis. Simpler, better measurements will be made, but these will only benefit the patients if the users become better educated in the fundamentals of new techniques.

The book is in general well illustrated and referenced. The similarity between numbering of references and figures in the text is irritating, as is the occasional illogical arrangement of illustrations. These are minor criticisms of an otherwise excellent, well balanced text which deserves to be read by all practising anaesthetists.

Sheila Willatts

Chronic Obstructive Pulmonary Disease. Edited by H. D. Montenegro. Published by Churchill-Livingstone, Edinburgh. Pp. 282; illustrated; indexed. Price £33.

This volume describes the latest developments in chronic bronchitis and emphysema which frequently overlap and are commonly described by the term chronic obstructive pulmonary disease (COPD). Although this disease is one of the main causes of mortality and morbidity in the Western world, there is a tendency to consider it the "poor relation" of chest medicine in view of the major limitations in treatment hitherto. If nothing else, this volume firmly debunks this approach and highlights the intellectual challenge which is currently present in research and treatment of COPD. It is one of an intended series on Respiratory Diseases which promises to be of interest to general and specialist clinicians, and advanced students.

The first three chapters relate to mechanisms leading to COPD, such as imbalance between connective tissue components, mainly proteases and protease inhibitors, abnormal mucociliary transport (with a description of the latest techniques available for its measurement) and hyperreactivity of the airways. The last of these is responsible for the reversible component of COPD, and the authors provide an interesting update on this subject, which is, of course, of major relevance in asthma. There follow chapters on control of breathing and the mechanisms of dyspnoea. Although interesting, these are rather less directly relevant, apart from the role of respiratory muscle fatigue in acute exacerbations of COPD, which is discussed in detail, including clinical and laboratory methods of detection. A chapter is devoted to haemodynamic events, including recent concepts regarding compressive mechanical heart–lung interaction during positive pressure breathing, which should be of particular interest to anaesthetists and other intensive care staff. The final two chapters deal very well with two current controversial areas of therapy, namely corticosteroid therapy in patients with COPD, and the principles and practical applications of exercise training, breathing training and ventilatory muscle training.

The volume is well presented, with frequent current references and no unnecessary graphic illustrations. It is also always practical and, in summary, is an excellent "state of the art" volume for those who are interested in the most recent developments in the management of COPD.

Chris J. Clark

Pain. (Proceedings of Joint Meeting of the European Chapters of the International Association for the Study of Pain, Abano Terme, May 1983.) Edited by R. Rizzi and M. Visentin. Published by Piccin/Butterworths. Pp. 488; illustrated; indexed.

This volume contains the scientific papers presented at the meeting, the rationale for which was to draw together interested participants from Eastern and Western Europe, and to foster the formation of associations in various European countries. The editors hope that the volume will be of interest to many health workers involved in pain research and therapy. The book is divided into three sections: Neck–Shoulder–Arm pain Syndrome, Pain in Children and Pain Control in Malignancies of the Vertebral Column.

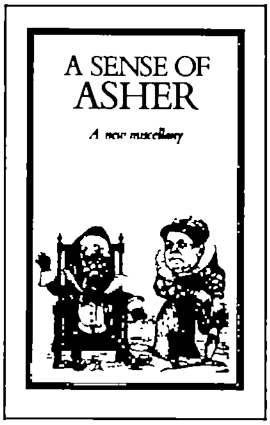
The first half of the book is devoted to the section on Neck–Shoulder–Arm pain and is divided into six logical subsections, namely Recent Diagnostic Methods, Clinical Aspects, Pharmacological Therapy, Physical Therapy, Anaesthesiological and Surgical Therapy, Psychological and other Non-Invasive Treatments. The organization is logical; however, the speakers/authors completely ignore each other's presentations. This is highlighted by the sub-section on Clinical Aspects, in that four of the five authors introduce four clinical syndromes which the succeeding 29 authors completely ignore. In addition, the succeeding authors introduce another 10 syndromes and it is patently obvious that all the syndromes mentioned are similar. The editors, R. Rizzi and M. Visentin, would have been better advised to keep the discussion to the broad topic of Pain in the Neck, Shoulder and Arm, without complicating it with many pleasant sounding syndromes. There is no discussion to inform the reader how to make these 15 diagnoses, or even how to choose the right treatment from the bewildering array which varies from Pulsed Magnetic Fields to Hypnotherapy.

The next section is titled Pain in Children and is divided into five subsections: Experimental and Clinical Pain, Psychological Aspects of Pain in Children, Headache in Children, Rheumatic and Orthopaedic Pain in Children, and Pain due to Malignancies in Children. This is the best of the three sections in the book because it has the most organized authors. The section on Malignancies is particularly good and it highlights why this subject has not had much written about it — malignant pain in children is uncommon. The sections on Headache and Rheumatic and Orthopaedic Pain are also good.

The final section is devoted to Pain Control in Malignancies of ther Vertebral Column and has two subsections, Conservative Therapy and Surgical Therapy. This section is similar in its disorganization to the first, underlined by the final paper on Neuroadenolysis of the Pituitary Gland, which was totally incomprehensible to the reviewer. In summary, this collection of papers presented at the Joint Meeting of the European Chapters of the I.A.P.S. in 1983 may have achieved its aim of getting the interested workers from East and West Europe together. However, because of the lack of organization and discussion of the various papers, the reviewer believes that it will be of little use to health workers involved in pain research and therapy, the section on Pain in Children excluded.

Chris Glynn

A SENSE OF ASHER



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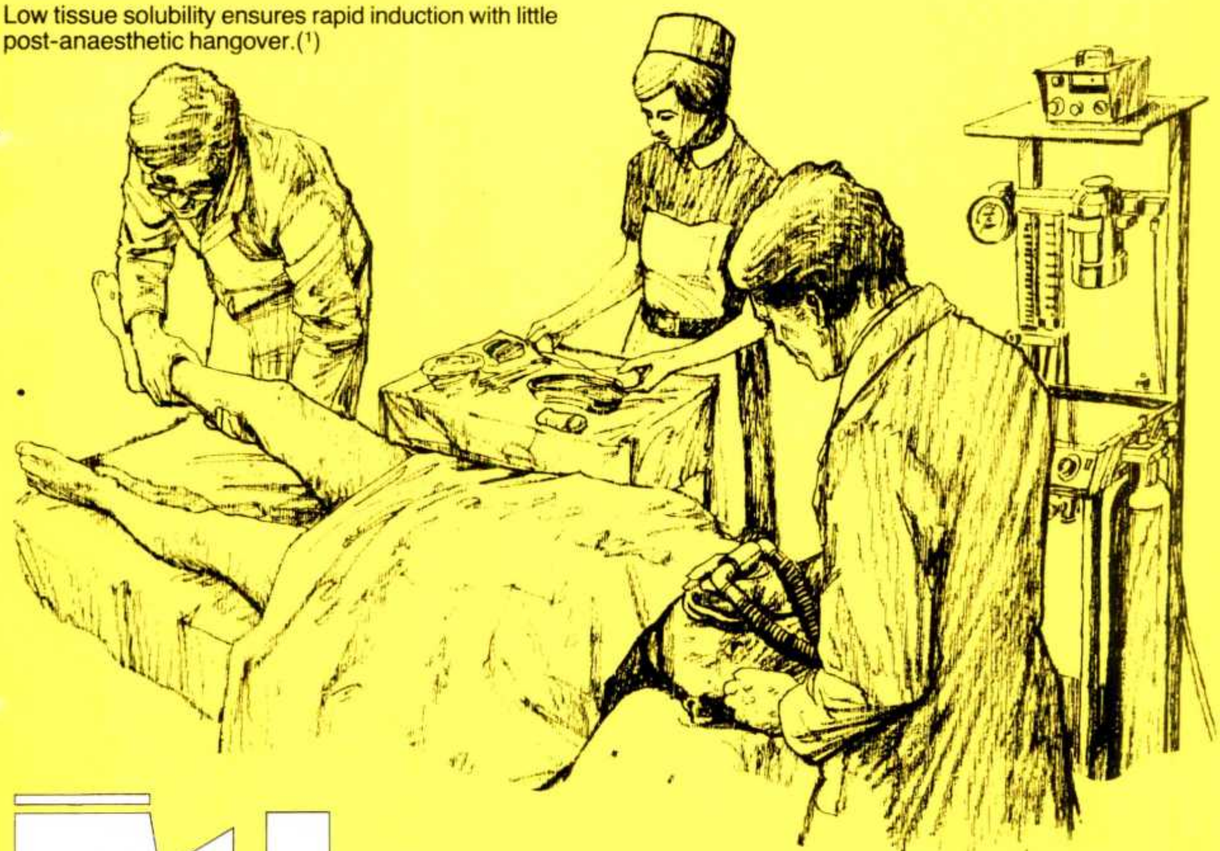

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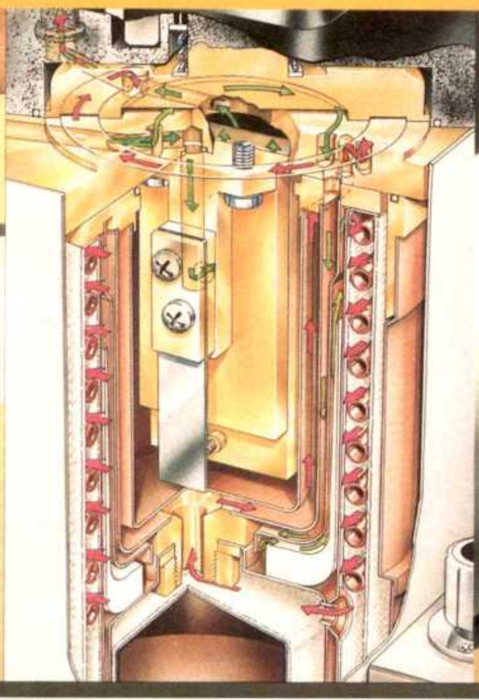

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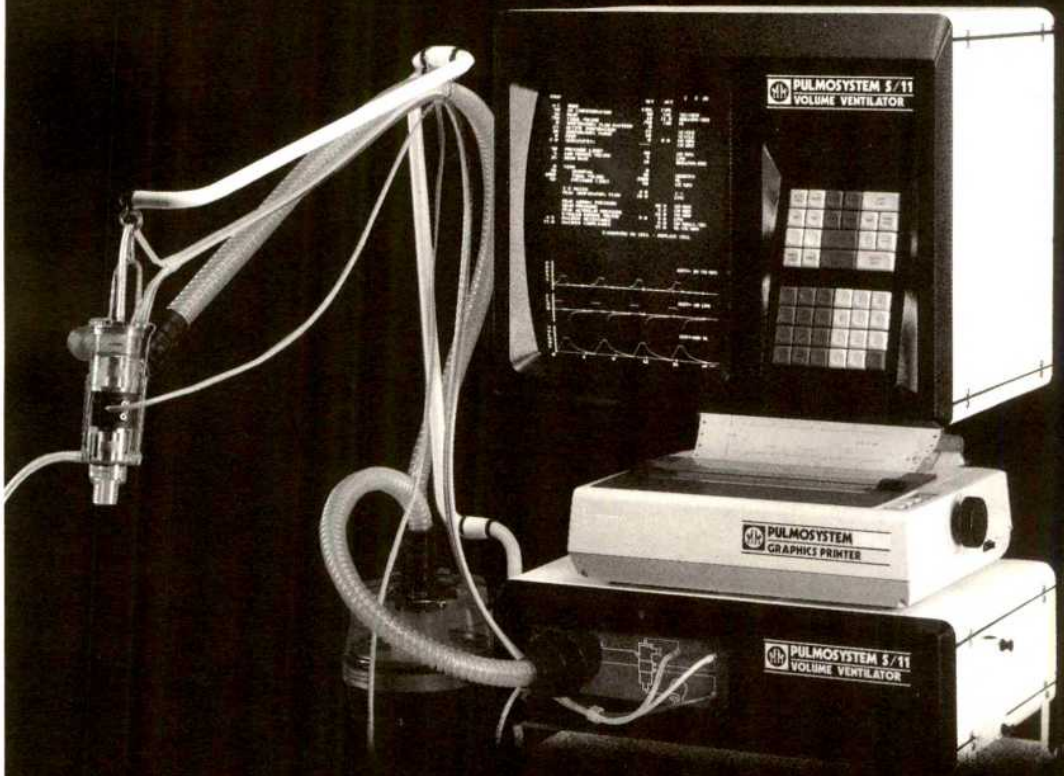

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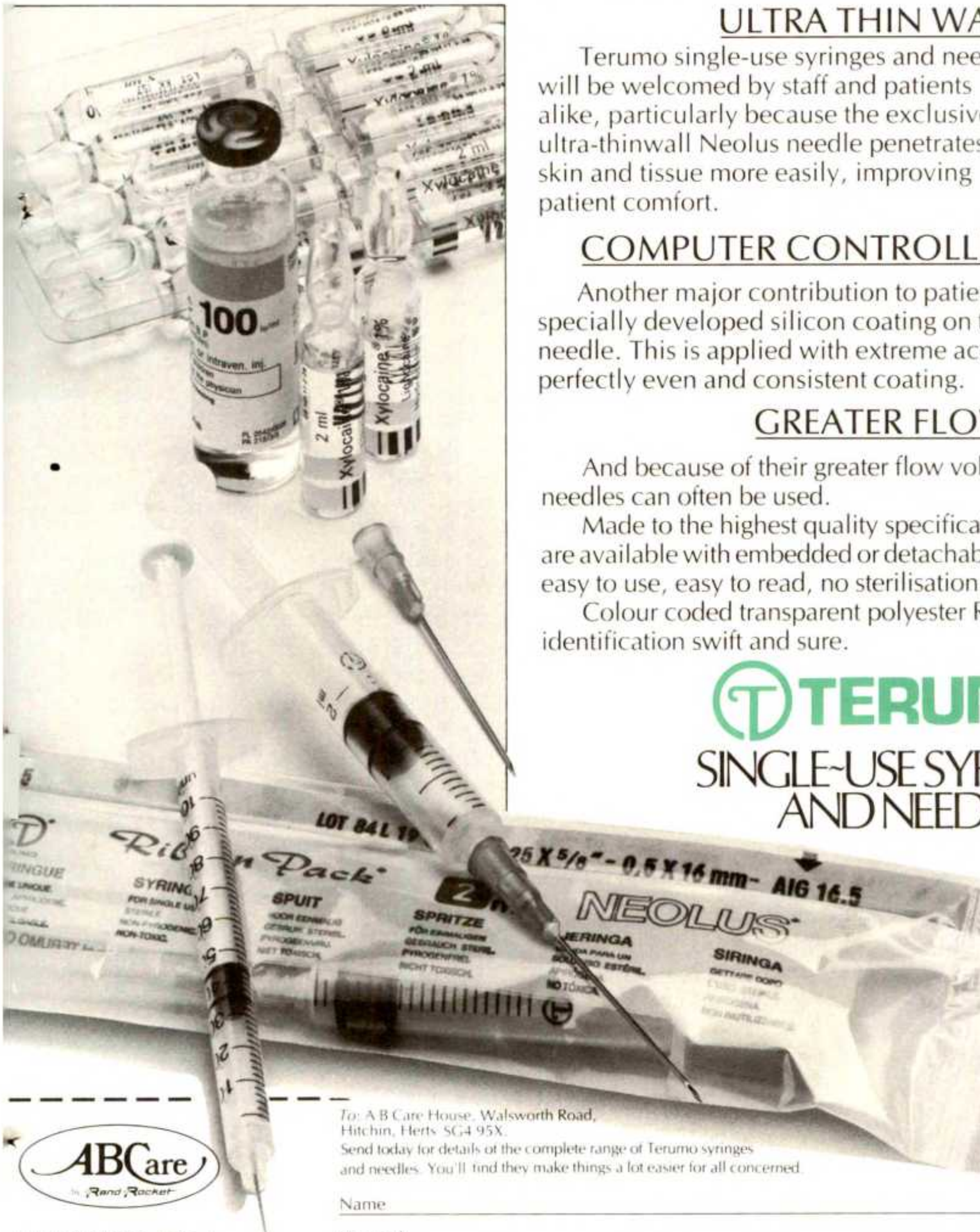

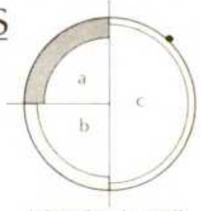

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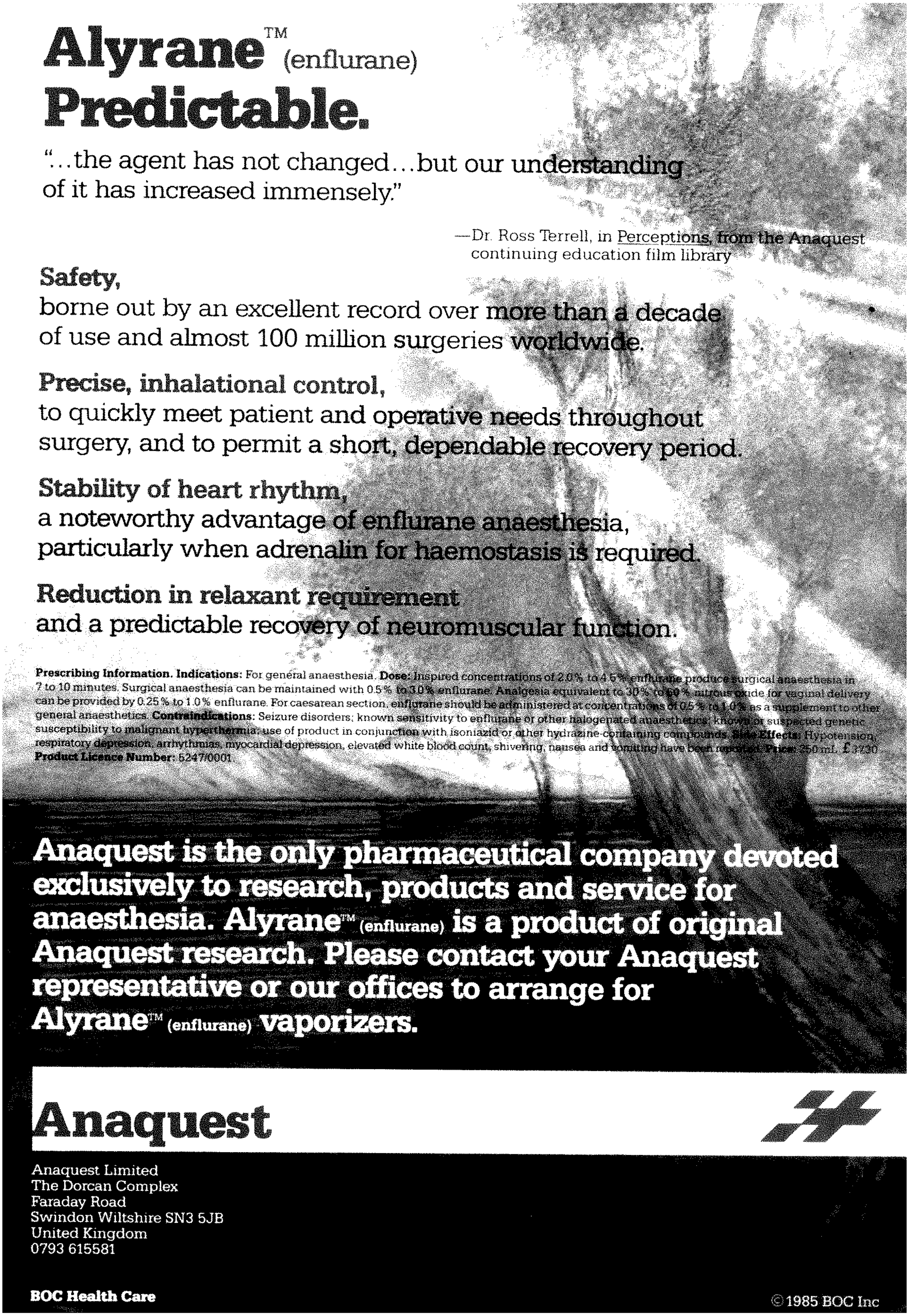

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DELETION

The following deletion has been made from the Eli Lilly Price List:

Product No.	*Product*	*Pack*
659	"Brietal" Sodium	5 g/35 ml vial
663	"Brietal" Sodium	2.5 g/17.5 ml vial

ERRATUM

Br. J. Anaesth. (1985), 57, 829P

In the abstract "Dosage and speed of onset of atracurium and vecuronium" (Healy et al.), the final sentence should read: "...0.05–0.06 mg kg^{-1} for vecuronium and 0.2–0.24 mg kg^{-1} for atracurium."

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

ACKNOWLEDGEMENTS

Each manuscript submitted to the *British Journal of Anaesthesia* is reviewed not only by members of the editorial staff but also by individuals not associated with the editorial staff who have particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaestheisa. Acceptance for publication is, consequently, based on the views of two or more individuals as to the originality, validity and clinical relevance of the information presented. At this point, the Editor would like to acknowledge sincerely the significant contributions made by the undernoted individuals who, in addition to the Editorial Board, reviewed manuscripts during 1985.

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QUANTITATIVE ASSESSMENT OF THE EFFECTIVENESS OF CHEMICAL LUMBAR SYMPATHECTOMY

P. T. McCOLLUM, V. A. SPENCE, B. MACRAE AND W. F. WALKER

SUMMARY

Twenty-one chemical sympathectomies were assessed in this study by taking infra-red thermograms of the feet before and after the procedure. Patients with relatively high perfusion pressures were shown to have the best response, while those with a low perfusion pressure had little or no increase in mean temperature in the foot.

The objective evaluation of the postoperative effect of a sympathectomy has received scant attention (Cousins et al., 1979), primarily because of the difficulty of measuring skin blood flow in the foot. The most obvious clinical response to a successful sympathectomy is a significant increase in skin temperature in the foot, an increase resulting entirely from an improvement in perfusion in the foot, mainly via A–V anastomoses. However, in some patients with critical limb ischaemia, the improvement in perfusion may be extremely marginal and the consequent increase in temperature may be either evenly distributed around the foot or localized to a particular segment. For this reason, a point source measurement with a thermistor, whether single or multiple, will not always provide an accurate indication of the changes in temperature. Furthermore, the accurate assessment of small changes in temperature is important before the adequacy of sympathetic blockade can be established.

For the past decade, we have used infra-red thermographic methods to study the longitudinal temperature gradients which exist in the lower limbs of patients with peripheral vascular ischaemia (Spence et al., 1984). Initially, resolution was poor and grey tone, qualitative images were all that could be obtained. At present, thermographic systems can be calibrated in absolute terms and interpreted quantitatively.

We report the use of a quantitative thermographic method to assess the adequacy of chemical sympathetic blockade carried out in patients with a range of peripheral vascular disorders.

PATIENTS AND METHODS

Twenty patients (10 females) were included in the study. Two patients underwent bilateral sympathectomy (carried out at different times), making a total of 22 sympathectomies available for assessment. The average age was 67.6 yr ± 11.1 (mean ± SD); four patients were diabetic.

A thermographic investigation along with ankle pressure measurements recorded by the Doppler method were undertaken in each patient. Patients were allowed to equilibrate for 20 min at a room temperature of 21 °C ± 1 °C and pre- and postoperative measurements were obtained at the same time of day for each patient. This ensured that potential variations in absolute temperature measurements were negligible, as experience with thermography has demonstrated that there is very little inter-daily variation between patients, provided they are allowed sufficient time to acclimatize in a controlled environment. Thermography was performed with a Philips Digital Thermograph and the images stored on disc in a Cromenco System 3 Microcomputer. Each thermographic image of the feet was described by 15 colours between underrange black (black level) and overrange white. A scale of 10 °C representing the 15 colours was chosen so that each colour represented a 0.67-°C isotherm. As the tempera-

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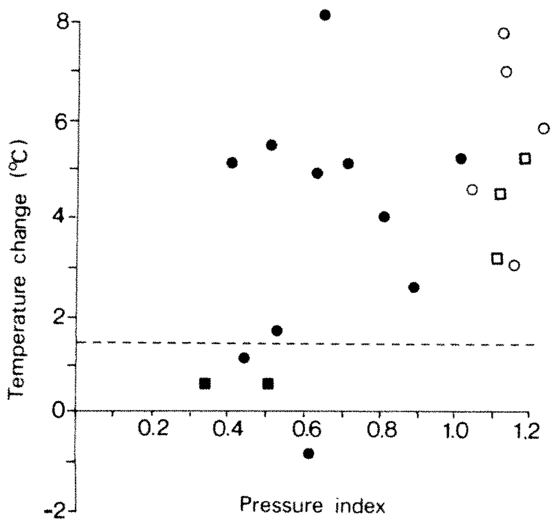


FIG. 1. Relationship of temperature change (*Y* axis) to ankle/arm pressure ratio (*X* axis). ■ = rest pain; ● = claudicant; ○ = vasospastic; □ = non-vascular.

ture of the black level is known in absolute terms, a software package was designed so that the temperature differences between the pre- and postoperative images could be determined. This was estimated by using the microcomputer to add together all the pixels in each colour band for the pre- and postsympathectomy images, to multiply this figure by the respective value for that colour band, and then to average out the mean value for the image.

Sympathectomy was carried out using percutaneous phenol under bi-plane radiological control, and was performed by or under the direct supervision of one operator (W.M.).

RESULTS

The mean change in foot temperature following sympathectomy is plotted against the pressure index (ankle pressure/arm pressure) for each subject in figure 1. One subject had incompressible vessels, so the ankle pressure could not be estimated and is not included in the figure. In 17 of 21 sympathectomies (81 %), the mean increase in the skin temperature in the foot was greater than 1.5 °C, indicating a positive response to the procedure. Three patients (14 %) had a temperature increase of between 0.5 °C and 1.5 °C, indicating a weak but positive response to the sympathectomy.

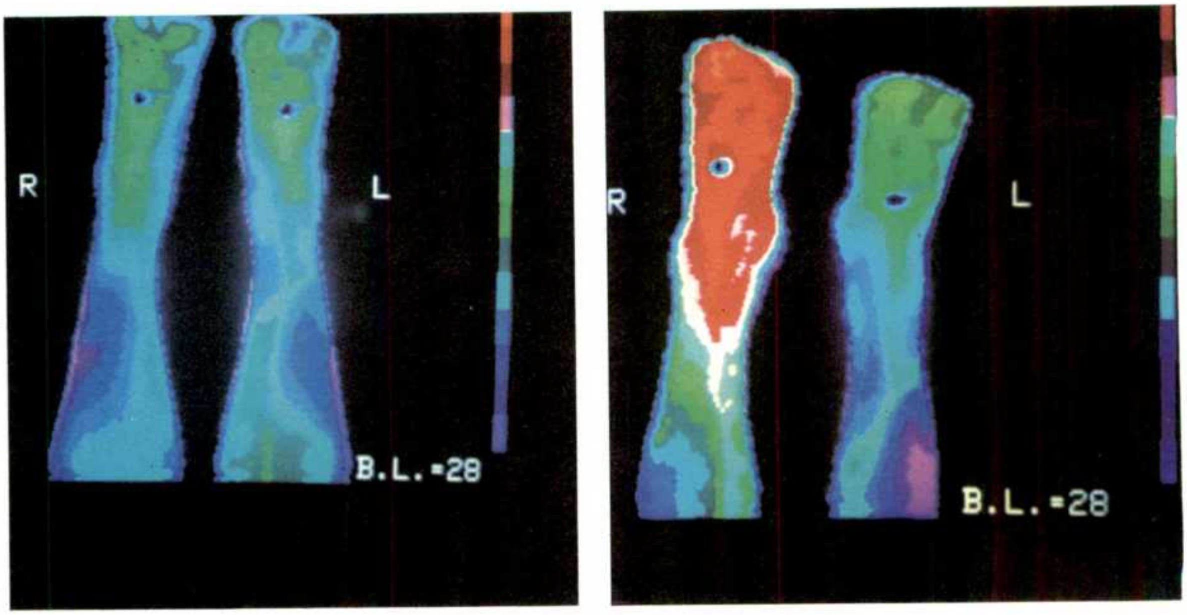
In table I the increases in temperature are presented in relation to the presenting symptoms. Clearly, vasospastic disorders (and "others") with normal pressure indices demonstrated the greatest increases in temperature whereas the patients with ulcers or rest pain and poor perfusion pressures, or all three, had the smallest temperature response.

DISCUSSION

A successful sympathectomy, by abolishing sympathetic tone, increases perfusion to the distal part of the limb with a consequent significant increase in skin temperature. If there is no obvious increase in skin temperature, then a sympathectomy may be deemed to be unsuccessful. With a chemical sympathectomy there may be two reasons for failure to increase perfusion in the foot: the sympathetic blockade may be incomplete or there may be no further potential for vasodilatation because the presence of ischaemia has already induced maximal vasodilatation locally. Whatever the cause, it is important to be able to assess objectively the effects of sympathetic blockade, so that the precise clinical and haemodynamic criteria needed to predict the outcome of sympathectomy can be ascertained. If such criteria are available, then the need to repeat the procedure in instances of possible incomplete sympathetic blockade can be determined. The thermographic method provides an accurate and quantifiable method of assessing the response to sympathectomy.

TABLE I. *Sympathectomy data (mean ± SD) related to indication for operation*

Group	*n*	Pressure index	Temperature (°C) Before op.	After op.	Temperature difference (°C)
Vasospastic	5	1.10 ± 0.05	27.0 ± 2.6	32.7 ± 1.1	5.7 ± 1.9
Claudicants	11	0.65 ± 0.19	26.4 ± 2.1	30.2 ± 1.7	3.7 ± 2.6
Ulcer/Rest pain	2	0.43 ± 0.11	26.9 ± 1.1	27.6 ± 1.1	1.0 ± 0.5
Others	3	1.13 ± 0.05	27.8 ± 0.6	32.1 ± 1.2	4.3 ± 1.0



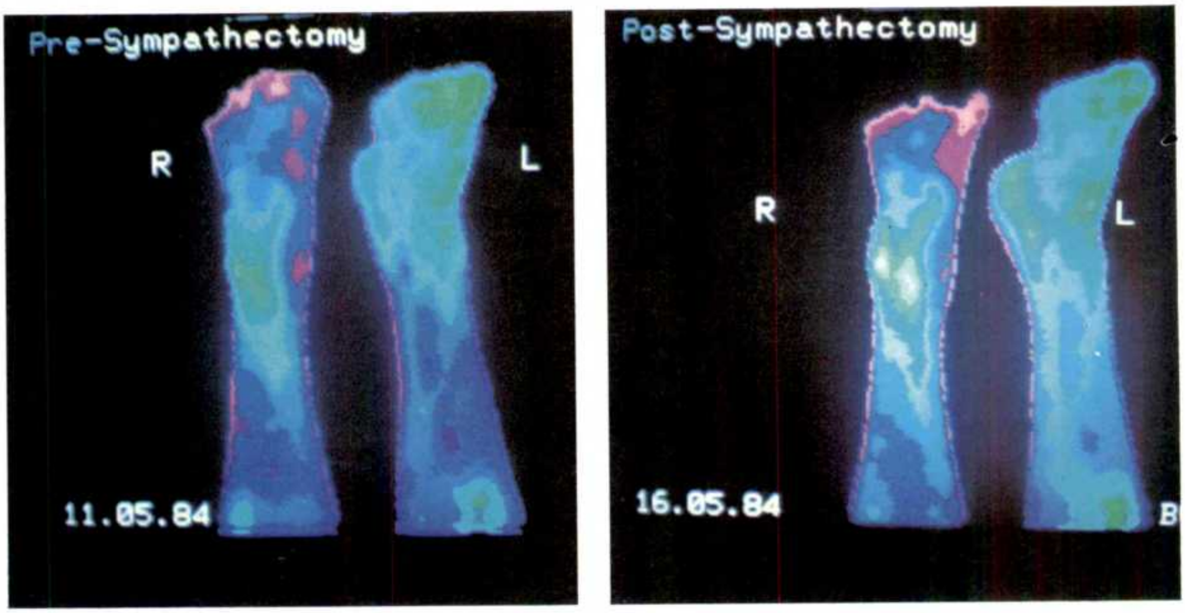


FIG. 2. Infra-red thermograms before (A) and after (B) a right-sided chemical sympathectomy. The thermograms are calibrated in absolute terms with 15 colours covering a range of 10 °C from black level (B.L.) at 28 °C to the white level at 38 °C. In this patient the mean temperature difference in the affected foot was 3.1 °C. Blue colours represent lower temperatures while red colours are warmer.

FIG. 3. Pre (A) and post (B) sympathectomy thermograms following a right-sided lumbar chemical sympathectomy in a patient with rest pain and ulceration of the right forefoot. The response to a sympathectomy has been poor, with an increase in mean foot skin temperature of only 0.5 °C. This temperature increase is localized to the proximal part of the foot with no change in temperature distally. The assessment of such a temperature change would be difficult by any other means.

It is not the place of this paper to discuss the merits and demerits of lumbar sympathectomy, which remains the treatment of choice for many vascular conditions, despite the lack of objective evidence of its efficacy (Kim, Arakawa and VonLintel, 1975). Rather, we have set out to describe a method which may be used to measure the completeness of the sympathectomy. The pulse wave monitor also offers this end-point (Breene and Eggers, 1974) but is, unfortunately, not quantifiable. The same argument can be used against the skin potential response (Cronin and Kirsner, 1979) and against sweat tests (Cousins et al., 1979). Despite this, these methods are useful and provide an indication of success or failure.

Plethysmographic studies, on the other hand, can provide a degree of quantitation (Courbier, Reggi and Jausseran, 1979), but suffer from considerable interpretative difficulties at the low perfusion pressures commonly seen in ischaemic limbs. However, where there is a reasonable perfusion pressure, plethysmography gives an excellent indication of the degree of response after sympathectomy and, when performed in these patients, correlated well with the mean increase in temperature. Doppler pressure measurements can be used to indicate those patients in whom a sympathectomy is more likely to succeed (Seeger, Lazarus and Albo, 1977; Plecha et al., 1980) but they cannot confirm successful completion or failure of the sympathectomy.

It is often suggested that diabetics should not have a sympathectomy performed as they may already have an "auto-sympathectomy" as a result of diabetic neuropathy. In some patients this neuropathy is seen as a "hot foot" on thermography and so unnecessary sympathectomy may be avoided. Of the four diabetics in the present series, one had a poor response but was in the rest-pain group, while the others had good responses. The numbers are too small for a definitive discussion, but the results suggest that sympathectomy may be of benefit in some diabetic patients with vascular disease.

In this study, patients with normal perfusion pressures in the foot and high sympathetic tone (e.g. Raynaud's types) had a significant response to chemical sympathectomy, the change in temperature in the foot being greater than 5 °C in some instances (fig. 2A, B). However, although patients with ischaemic rest pain with a low distal perfusion pressure may have an increase in skin temperature in the foot following sympathectomy, this may be localized to a specific area of skin. This phenomenon is readily appreciated on examination of the thermograms in figure 3A and B. Thus, it is important not only to derive a mean temperature change for the area as a whole, but also to assess the overall thermogram, before conclusions regarding the results of therapeutic measures are made.

The thermographic method is unique in its ability to detect and quantify such changes, and is the most appropriate of the available techniques for determining the changes in perfusion in the foot which occur after sympathectomy. It is hoped that such a system will permit a more rational approach to the selection of patients for chemical sympathectomy.

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RELATIONSHIPS BETWEEN INSPIRED OXYGEN CONCENTRATION AND VENOUS ADMIXTURE DURING NITROUS OXIDE–OXYGEN–HALOTHANE ANAESTHESIA

J. H. KERR, P. FOEX AND D. A. PYBUS

SUMMARY

The inspired oxygen concentration ($F_{I_{O_2}}$) was changed on 43 occasions at about 30-min intervals in 13 patients during artificial ventilation with mixtures of nitrous oxide (N_2O), oxygen and halothane. Ventilator settings remained unchanged for each patient and at the end of each period, samples of arterial and central venous blood (and, in six patients, pulmonary arterial blood) and inspired and expired gases were collected. Oxygen tension was measured with a dedicated electrode shown to be unaffected by N_2O. Venous admixture ($\dot{Q}va/\dot{Q}t$) was calculated at each $F_{I_{O_2}}$. There was a highly significant correlation between the direction of change of $F_{I_{O_2}}$ and that of $\dot{Q}va/\dot{Q}t$, irrespective of whether $F_{I_{O_2}}$ increased or decreased. In 10 patients, there was a progressive increase in $\dot{Q}va/\dot{Q}t$ as $F_{I_{O_2}}$ increased above 40%, and in all patients $\dot{Q}va/\dot{Q}t$ on nearly 100% oxygen was greater than that measured at the next lowest concentration (60–80%). These results are at variance with the pattern of behaviour predicted from the "critical Va/Q" theory and support the concept of an oxygen-dependent redistribution of perfusion.

The tendency for venous admixture (Qva/Qt) to increase at high fractional inspired oxygen concentrations (FI_{O_2}) has been demonstrated frequently within the past decade (McAslan et al., 1973; Kerr, 1975; Suter, Fairley and Schlobohm, 1975; Douglas et al., 1976; Drummond, Wildsmith and Masson, 1978; Reines and Civetta, 1979; Douglas, Downs and Snook, 1980; Oliven, Abinader and Bursztein, 1980; Quan et al., 1980; Shapiro et al., 1980) and this finding has been accompanied by the realization that changes must be occurring within the lungs as the FI_{O_2} is altered (Kerr, 1975).

Whether such changes are primarily the result of a redistribution of ventilation or of perfusion has yet to be established but, by measuring continuous ventilation:perfusion (Va/Q) ratio distributions within the lung, Wagner and colleagues were able to confirm that intrapulmonary shunting increased after pure oxygen breathing in subjects with normal (Wagner et al., 1974) and abnormal (Wagner et al., 1977) respiratory function. As a result of this work, Dantzker, Wagner and West (1975) hypothesized that the changes in venous admixture occur primarily as a result of a redistribution of ventilation. They described a parallel compartment, multiple unit, computer model of the lung in which the dispersion of the Va/Q ratios was log normal and in which the degree of dispersion (and many other variables) could be manipulated by the investigator. Using this model, the authors extended the concept of absorption atelectasis and introduced that of "critical Va/Q"—a ventilation:perfusion ratio at which expiration from the alveolar unit ceased because all the inspired gases had been absorbed by the blood flow. In units with Va/Q ratios below the critical value, the volume of gas entering during inspiration would be less than that carried away by the blood flow, so that such units would tend to collapse and thereafter contribute to the measured venous admixture. During inspiration of mixtures of nitrogen and oxygen, the critical Va/Q ratio will increase as FI_{O_2} is increased from 0.2 to 1.0 with a consequent increase in Qva/Qt

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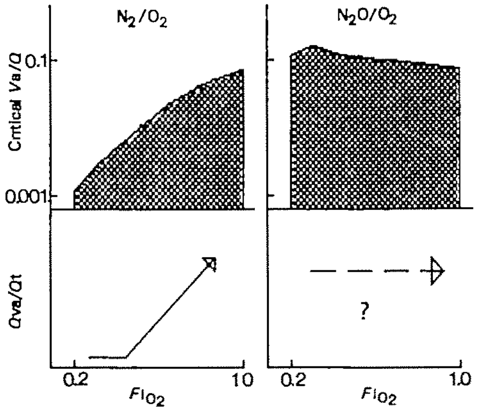

FIG. 1. Upper diagrams illustrate the relationship between "Critical $\dot{V}a/\dot{Q}$" and $F\text{I}_{O_2}$ when the balancing gas is nitrogen (on left) and nitrous oxide (on right). With N_2/O_2 mixtures, lung units with sub-critical $\dot{V}a/\dot{Q}$ ratios (shown by hatched areas) will tend to collapse as $F\text{I}_{O_2}$ increases and so produce an increase in $\dot{Q}va/\dot{Q}t$ as indicated in the lower left diagram. With N_2O/O_2 mixtures, the tendency to collapse does not alter significantly as $F\text{I}_{O_2}$ increases, and one would not expect there to be a change in $\dot{Q}va/\dot{Q}t$ from this cause as $F\text{I}_{O_2}$ increases (lower right diagram).

which is particularly apparent in the $F\text{I}_{O_2}$ range 0.5–1.0 and in inefficient lungs containing many poorly ventilated alveoli (fig. 1). This predicted increase in $\dot{Q}va/\dot{Q}t$ does not require an active physiological response to oxygen, since it can be explained on the basis of the differing solubilities of the constituent alveolar gases. The authors went on to suggest that substitution of the relatively insoluble balancing gas (N_2) with a more soluble gas (N_2O) at the same fractional concentration would further increase the critical $\dot{V}a/\dot{Q}$. They calculated that the critical $\dot{V}a/\dot{Q}$ would remain essentially unchanged as $F\text{I}_{O_2}$ was increased from 0.4 to 1.0 (fig. 1). By implication, therefore, it can be predicted that the usual oxygen-dependent increase in $\dot{Q}va/\dot{Q}t$ seen with N_2/O_2 mixtures should be absent if N_2O was the balancing gas.

The present study was devised to test this prediction and to provide further information about the mechanisms responsible for the increases in $\dot{Q}va/\dot{Q}t$ often seen at high values of $F\text{I}_{O_2}$.

PATIENTS AND METHODS

Patient selection and anaesthetic technique

Thirteen patients were studied during elective, non-thoracic vascular surgery. All patients had given informed consent for the investigation and the study had the approval of the Hospital's Research Ethics Committee. Twelve of the patients were smokers and had smoked at least 10 cigarettes per day for 5 years before surgery. The 13th patient was a non-smoker, but had a history of dust exposure and had the clinical signs of Chronic Obstructive Airways Disease. At the time of surgery, none of the patients had significant sputum production, or was limited in activity by respiratory symptoms. Details of the patients are contained in table I.

Approximately 1 h before arrival in the anaesthetic room, the patients were premedicated with papaveretum and hyoscine. Anaesthesia was induced with thiopentone and tracheal intubation was facilitated with pancuronium. Ventilation of the lungs was commenced with a gas mixture of nitrous oxide, oxygen and halothane using a volume pre-set ventilator (Penlon "Oxford") in a non-rebreathing mode at a frequency of 10 b.p.m.

TABLE I. *Biographical data, smoking history and operative details of the 13 patients*

Subject	Sex	Age (yr)	Weight (kg)	Cigarettes /day	Operation
1	F	55	74	20	Aorto–iliac endarterectomy
2	M	61	62	20	Femoro–popliteal bypass
3	M	52	68	15	Aorto–iliac endarterectomy
4	M	52	80	10	Femoro-popliteal bypass
5	M	56	72	20	Femoro–popliteal bypass
6	F	58	51	10	Femoro-popliteal bypass
7	M	60	67	20	Aorto–iliac endarterectomy
8	M	59	77	10	Aortic aneurysm repair
9	M	43	75	40	Aorto–iliac endarterectomy
10	M	51	72	40	Aorto–iliac endarterectomy
11	M	62	60	35	Femoro–popliteal bypass
12	M	69	74	Nil	Aortic aneurysm repair
13	M	54	89	20	Aortic aneurysm repair

Tidal volume was set in the range 8–12 ml/kg body weight and measured with a Wright's respirometer. These ventilator settings were not altered during the course of the study. A cannula was inserted to the radial artery to permit the continuous monitoring of arterial pressure, and for the sampling of arterial blood. In six patients, a flow-directed catheter was passed into a pulmonary artery, correct placement being confirmed by recognition of the typical waveform. In the remaining seven patients a central venous catheter was placed so that its tip was estimated to lie in the superior vena cava. Nasopharyngeal temperature was monitored continuously. Anaesthesia was maintained by the continuous administration of 0.5–1.0% halothane while the inspired oxygen and nitrous oxide concentrations were varied in accordance with the design of the investigation. As far as was possible a constant FI_{hal} was maintained throughout the period of study, although it was occasionally necessary to alter the concentration if unacceptable hyper- or hypo-tension occurred. Muscle relaxation was maintained with incremental doses of pancuronium and a few patients were given bolus doses of fentanyl 50–100 µg. Fluid requirements were met in most patients by the infusion of Hartmann's solution, although blood was replaced when indicated clinically. Body temperature was stabilized by the use of warming blankets and the warming of all i.v. fluids.

Design of investigation

During the course of the procedure the lungs of each patient were ventilated with at least four different gas mixtures in sequence (oxygen at an approximate concentration of 30, 50, 75 or 99%, halothane in the range 0.5–1.0% and nitrous oxide as the balance). The order of administration of the mixtures was varied from patient to patient and is shown in table II. After an equilibration period of 30 min, 5-ml specimens of arterial, central venous and, where available, pulmonary artery blood were taken anaerobically into plastic syringes and placed immediately in iced water before analysis. A specimen of inspired gas was taken and a 2-min sample of expired gas was collected in a Douglas bag which had been evacuated previously to a sub-atmospheric pressure of 20 mm Hg. Subsequently, three determinations of cardiac output ($\dot{Q}t$) were made using a dye dilution technique. Once all the measurements had been obtained, a new FI_{O_2} was selected and the cycle of observations was repeated.

Analytical techniques

Measurements of oxygen tension were made at 37 °C using a platinum cathode (Clarke type) polarographic electrode filled with modified electrolyte (Schuler, 1966). Polarography with this electrode had shown that its readings were unaffected by gas mixtures containing nitrous oxide or halothane and that, if polarized at −800 mV, it gave a steady reading within 1 min of a change of sample. This dedicated electrode was operated by an experienced technician and was calibrated with an oxygen-free mixture ("white spot" nitrogen) and with an oxygen-in-nitrogen mixture (50%), the composition of which had been measured using a carefully calibrated paramagnetic oxygen analyser (Nunn et al., 1964). The calibration of the electrode was verified before and after each blood sample using the 50% mixture and the reading corrected to take into account any difference in the calibration measurements ("drift correction"). Potential errors from differences in the measurement in the blood and gas phases were minimized by the application of "blood-gas" factors which had been estimated over the entire range of PO_2 using tonometered whole blood. PO_2 values of less than 15 kPa were multiplied by 1.03, those between 15 and 38 kPa by 1.05 and those greater than 38 kPa by 1.09. Finally, a "time correction" factor, which related to both the elapsed time and the measured PO_2, was applied (Kelman and Nunn, 1966). The maximum interval between sampling and analysis for all samples was 15 min and, since arterial samples were analysed first, was considerably shorter for those with high PO_2 values. Corrections for differences in temperature between the patient and the electrode were not applied. PCO_2 and pH were determined using conventional electrodes (Radiometer).

Inspired and expired oxygen concentrations were measured with a paramagnetic analyser (Servomex) which had been calibrated with air and 100% oxygen. The volume of the expired gas was measured at room temperature with a dry gas meter and subsequently converted to BTPS using standard equations. Expired carbon dioxide analysis was performed on the electrode system. Haemoglobin concentration was measured on the first specimen obtained and the value obtained was used in all subsequent calculations of blood oxygen content.

At high inspired oxygen concentrations, alveolar

TABLE II. *Measured and derived values from the 13 patients. Results are given in the order in which they were collected*

		Pa_{O_2}	Pa_{CO_2}	$P\bar{v}_{O_2}$(kPa)		$\dot{Q}va/\dot{Q}t$ (%)	
Subject	FI_{O_2}	(kPa)	(kPa)	PA	CV	PA	CV
1	0.260	12.5	4.20		6.25		15.4
	0.990	59.0	3.60		6.27		15.5
	0.595	38.2	4.00		4.93		5.7
	0.354	23.5	4.30		5.05		3.0
2	0.289	12.0	4.99		5.87		16.1
	0.993	57.0	3.62		5.74		13.0
	0.395	24.8	3.91		5.64		4.8
	0.778	45.0	4.00		6.05		12.4
	0.544	34.0	3.80		5.80		7.9
3	0.995	71.0	4.67	7.28	7.80	11.3	12.3
	0.695	53.0	4.30	6.35	6.06	4.4	4.0
	0.315	22.0	4.39	5.60	5.45	2.1	2.0
	0.491	35.0	4.53	4.87	4.43	2.6	2.1
4	0.993	59.0	3.45	7.60		21.2	
	0.517	33.0	3.50	5.90		6.4	
	0.309	21.0	3.60	5.73		3.4	
	0.756	49.0	3.20	6.22		10.7	
	0.432	31.5	3.60	6.00		2.6	
5	0.436	28.6	5.03		7.23		8.9
	0.289	14.0	4.62		5.65		10.3
	0.995	72.0	4.75		6.67		9.5
	0.720	56.0	5.98		8.52		5.6
	0.543	42.0	6.04		8.55		5.0
	0.345	20.5	5.47		7.24		10.4
6	0.302	14.6	3.84	6.08	6.14	12.6	12.8
	0.991	55.0	3.44	6.20	6.25	16.7	16.3
	0.754	49.0	4.08	8.30	8.40	15.6	15.5
	0.512	32.5	4.59	6.36	6.78	6.9	8.1
7	0.315	23.5	4.24		9.60		9.0
	0.990	67.0	4.19		7.18		12.1
	0.625	44.0	4.45		7.73		10.3
	0.452	30.0	4.50		8.27		10.7
8	0.309	13.6	5.61		6.26		17.5
	0.982	49.9	4.68		5.53		17.6
	0.664	41.0	6.61		8.44		13.6
	0.525	21.0	5.52		7.41		24.0
9	0.483	22.5	5.29	6.51	7.43	13.3	16.8
	0.985	57.0	6.71	8.05	9.0	17.2	19.8
	0.739	46.5	5.58	6.73	6.88	9.8	10.1
	0.319	19.0	6.14	8.10	9.30	9.7	13.3
10	0.500	28.2	5.30		7.81		13.6
	0.990	61.0	5.42		6.44		11.6
	0.715	48.0	6.94		8.75		9.3
	0.300	17.5	6.57		8.65		12.5
11	0.470	31.5	4.51		6.25		4.6
	0.990	65.0	4.56		6.74		11.3
	0.750	46.0	4.77		6.57		11.0
	0.315	23.0	5.09		6.37		2.8
12	0.510	34.0	4.45	4.70	5.24	3.7	4.2
	0.740	50.0	4.71	5.04	5.56	6.3	7.1
	0.995	68.5	4.91	5.89	7.28	10.6	14.2
	0.315	24.0	5.47	4.81	5.17	0.4	0.4
13	0.340	8.9	5.87	6.03		37.5	
	0.995	15.5	4.89	5.81	6.88	28.6	35.0
	0.765	12.1	5.13	5.06	5.36	22.5	23.9
	0.525	10.1	5.88	5.09	6.11	24.9	38.4

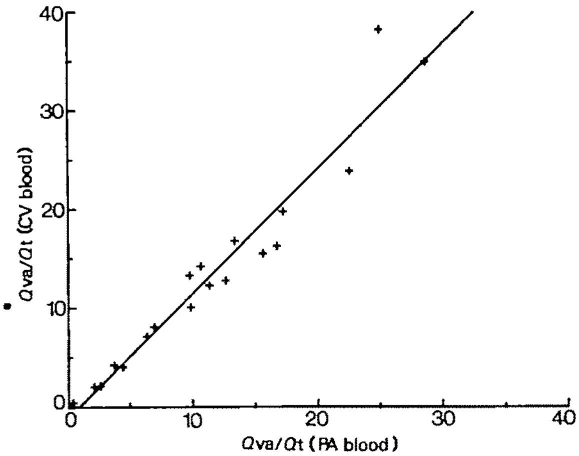

FIG. 2. Comparison of $\dot{Q}va/\dot{Q}t$ calculated using venous oxygen values measured on central venous (CV) blood with $\dot{Q}va/\dot{Q}t$ calculated using samples taken simultaneously from the pulmonary artery (PA) in five patients. The regression line is shown as a solid line: its slope = 1.27; intercept $Y' = -1.19$; square of the correlation coefficient = 0.9400.

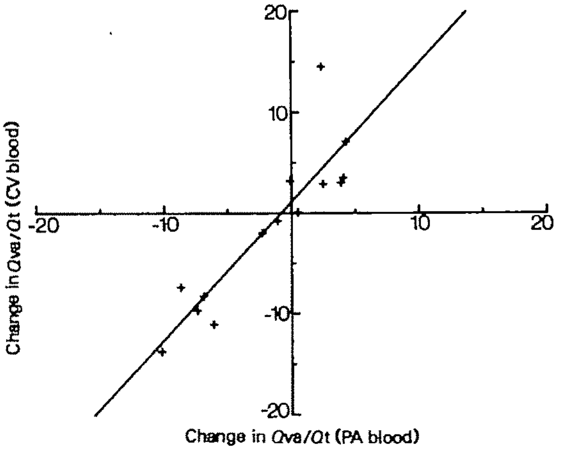

FIG. 3. Comparison of the change in $\dot{Q}va/\dot{Q}t$ following an alteration in $F_{I_{O_2}}$ calculated using venous oxygen values from simultaneous central venous (CV) and pulmonary artery (PA) blood samples. The effects of 14 changes in $F_{I_{O_2}}$ are compared from five patients. The regression line is shown as a solid line: its slope = 1.37; intercept $Y' = 1.125$; square of the correlation coefficient = 0.7987.

P_{O_2} was calculated using the classical "Alveolar Air Equation", but at the lower fractional concentrations (< 0.80), an equation which is suitable for use in the presence of nitrous oxide (Filley, Macintosh and Wright, 1954) was applied. Oxygen content of the blood samples was derived from the corrected blood gas values using the Kelman algorithm (Kelman, 1966) and an oxygen combining factor of 1.34. The standard "shunt" equation was used to calculate venous admixture (Berggren, 1942). The equations which form the basis for the various correction factors and content calculations have been described fully in an earlier study from this department (Foëx, Meloche and Prys-Roberts, 1971).

Statistical techniques

The results were analysed using Fisher's exact test, Friedman's two-way analysis of variance and linear regression analysis. Pooled data are presented in the text and tables as the mean ±SD and P values of < 0.05 were considered significant.

RESULTS

Table II contains details of the blood-gas measurements and the determinations of venous admixture undertaken in the 13 patients. In five patients from whom we obtained paired samples of pulmonary arterial (PA) and central venous (CV) blood, there was a good correlation between the values of venous admixture calculated using the different venous specimens, but the central venous blood tended to give a higher value (fig. 2).

Similarly, following an alteration in $F_{I_{O_2}}$, $\dot{Q}va/\dot{Q}t$ changed in the same direction whether estimated from pulmonary artery or central venous blood. Again, the size of the change in $\dot{Q}va/\dot{Q}t$ tended to be greater when calculated from central venous blood (fig. 3).

In the patients monitored with pulmonary artery catheters, we have used the pulmonary arterial values of $C\bar{v}_{O_2}$ for all subsequent analyses and graphical representations.

In table III we have documented the mean values of other variables which could have affected venous admixture. Analysis of variance failed to demonstrate any significant differences in mean arterial pressure, cardiac output, Pa_{CO_2}, or $P\bar{v}_{O_2}$ in the four ranges of fractional concentration of oxygen, neither were there any significant metabolic acid–base disturbances. To investigate further the relationship between cardiac output and $\dot{Q}va/\dot{Q}t$, the directions of change of the two variables were calculated on 43 occasions when the $F_{I_{O_2}}$ had been altered. Associated with 22 increases in cardiac output were 11 increases and 11 decreases in $\dot{Q}va/\dot{Q}t$, while the 21 reductions in

TABLE III. *Mean values (±SD) of arterial pressure, cardiac output, mixed venous* P_{O_2} *and arterial* P_{CO_2} *in the four ranges of* $F_{I_{O_2}}$

	$F_{I_{O_2}}$			
	0.2–0.39	0.4–0.59	0.6–0.79	0.8–0.99
Mean arterial	90.9	84.5	88.7	92.7
pressure (mm Hg)	(14.5)	(15.1)	(19.5)	(12.7)
Cardiac output	3.77	3.59	3.68	3.42
(litre min^{-1})	(1.17)	(1.12)	(1.16)	(1.18)
Mixed venous	6.43	6.38	6.98	6.57
P_{O_2} (kPa)	(1.31)	(1.24)	(1.33)	(0.77)
Arterial P_{CO_2}	4.89	4.70	4.98	4.53
(kPa)	(0.89)	(0.79)	(1.15)	(0.91)

TABLE IV. *Directions of change in* $F_{I_{O_2}}$ *and subsequent direction of change in Qva/Qt (a) in all subjects, (b) in those in whom both* $F_{I_{O_2}}$ *were greater than 0.4 and (c) in those in whom at least one* $F_{I_{O_2}}$ *was less than 0.4. Figures in parentheses are those derived from measurements on pulmonary artery (as opposed to central venous) blood*

	*Q*va/*Q*t UP	*Q*va/*Q*t DOWN	*P*
(a) All changes			
$F_{I_{O_2}}$ UP	11 (6)	4 (1)	0.0012
$F_{I_{O_2}}$ DOWN	6 (1)	21 (11)	
(b) Both $F_{I_{O_2}} > 0.4$			
$F_{I_{O_2}}$ UP	4 (3)	1 (0)	0.017
$F_{I_{O_2}}$ DOWN	3 (1)	14 (7)	
(c) At least one $F_{I_{O_2}} < 0.4$			
$F_{I_{O_2}}$ UP	7 (3)	3 (1)	0.056
$F_{I_{O_2}}$ DOWN	3 (0)	8 (4)	

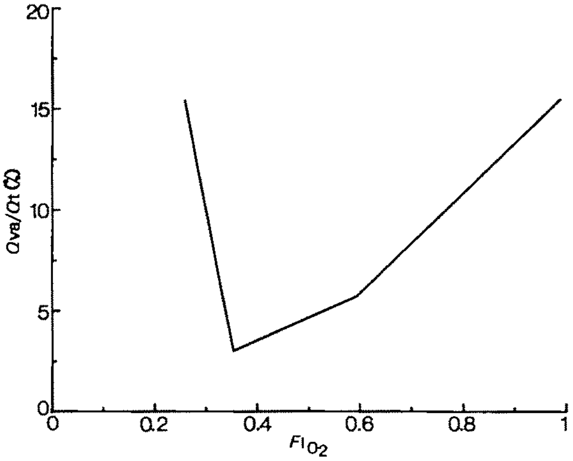

FIG. 4. Relationship between *Q*va/*Q*t and $F_{I_{O_2}}$ for patient 1. In figures 4, 5 and 6, values are plotted in order of ascending $F_{I_{O_2}}$ rather than in order of collection (see table II).

cardiac output were accompanied by seven increases and 14 decreases in *Q*va/*Q*t.

In total we examined the effect of 43 changes in $F_{I_{O_2}}$ in the 13 patients. On 15 occasions $F_{I_{O_2}}$ was increased from its previous value and in the remaining 28 it was reduced. There was a highly significant correlation between the direction of change in $F_{I_{O_2}}$ and the direction of change in *Q*va/*Q*t ($P < 0.001$) and this correlation held irrespective of whether $F_{I_{O_2}}$ was increased or decreased. If one considered only those changes of $F_{I_{O_2}}$ where one of the fractional concentrations was less than 0.4, then the significance of this relationship was lost although the tendency remained. In the remaining patients—involving changes in $F_{I_{O_2}}$ above 0.4—there was again a highly significant correlation between the direction of change in $F_{I_{O_2}}$ and the direction of change in *Q*va/*Q*t. These relationships are shown as contingency tables in table IV.

We identified three patterns of response to a changing $F_{I_{O_2}}$. Six patients demonstrated a curvilinear relationship between $F_{I_{O_2}}$ and *Q*va/*Q*t. In four of these six patients, *Q*va/*Q*t was highest at the lowest $F_{I_{O_2}}$, decreased as $F_{I_{O_2}}$ was increased to 0.4–0.6 and then increased again as $F_{I_{O_2}}$ approached unity. Patient 1 (fig. 4) typifies this pattern of response. Four patients demonstrated a

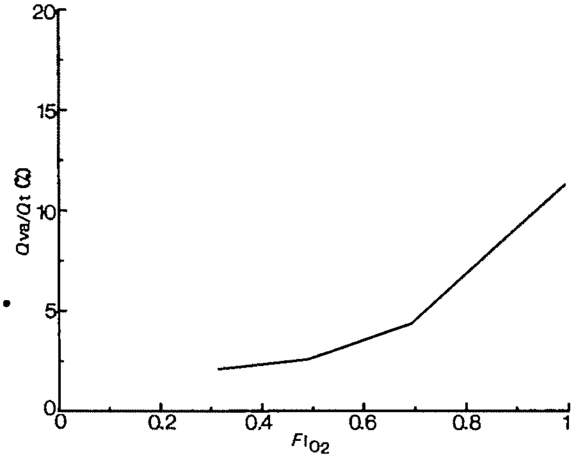

FIG. 5. Relationship between Qva/Qt and $F\text{I}_{\text{O}_2}$ for patient 3.

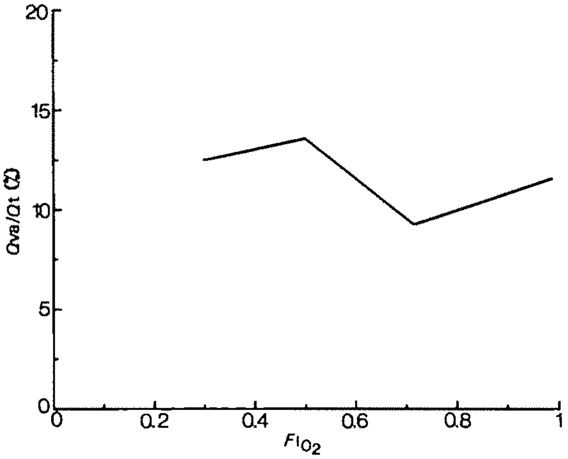

FIG. 6. Relationship between Qva/Qt and $F\text{I}_{\text{O}_2}$ for patient 10.

progressive increase in venous admixture as the fractional concentration of oxygen was increased and this is illustrated by the response of patient 3 (fig. 5). The final pattern was shown by three subjects in whom there was a sigmoid relationship between $F\text{I}_{\text{O}_2}$ and Qva/Qt, as is seen in the case of subject 10 (fig. 6).

In figure 7 we have expressed Qva/Qt as a percentage of the value which we obtained at the highest $F\text{I}_{\text{O}_2}$. As can be seen, on all occasions Qva/Qt at this $F\text{I}_{\text{O}_2}$ was greater than that measured when the fractional concentration was in the range 0.6–0.79 and in eight of the patients it was also greater than that measured in the range 0.4–0.59. We obtained the highest estimate of Qva/Qt during ventilation at the highest $F\text{I}_{\text{O}_2}$ in eight of the 13 patients and in the remaining five patients the maximal Qva/Qt was seen at some other $F\text{I}_{\text{O}_2}$— usually in the range of 0.2–0.39.

DISCUSSION

The principal finding of this study has been the demonstration of a consistent relationship between fractional inspired oxygen concentration and venous admixture during mechanical ventilation with mixtures of nitrous oxide in oxygen. In all 13 patients Qva/Qt increased as $F\text{I}_{\text{O}_2}$ was increased from 0.75 to 0.99. In the middle ranges of $F\text{I}_{\text{O}_2}$ this tendency for Qva/Qt to increase with increasing $F\text{I}_{\text{O}_2}$ persisted, but in the lower ranges of $F\text{I}_{\text{O}_2}$ the trend was reversed. Before considering the implications of this finding in detail, we propose to discuss various aspects of the methodology and experimental design.

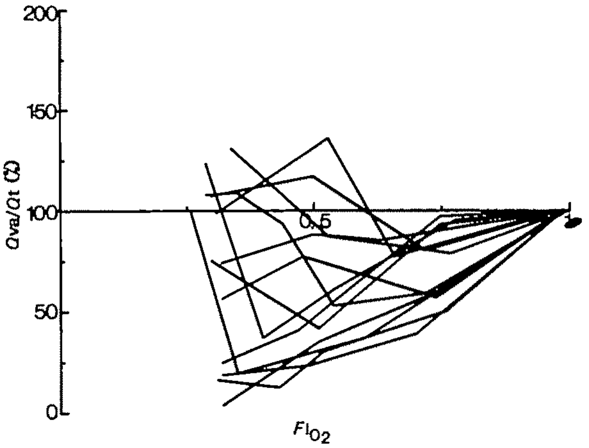

FIG. 7. Qva/Qt expressed as a percentage of Qva/Qt measured at an $F\text{I}_{\text{O}_2}$ of nearly 1.0. Each line represents the values from one patient and measurements have been plotted in order of ascending $F\text{I}_{\text{O}_2}$. According to "classical" physiological theory, Qva/Qt should be at its lowest when the $F\text{I}_{\text{O}_2}$ is 1.0 and should increase as $F\text{I}_{\text{O}_2}$ decreases. The "critical Va/Q" theory suggests that little change in Qva/Qt would be expected as $F\text{I}_{\text{O}_2}$ is altered.

Methodology

The results of this study are obviously crucially dependent on the accuracy of the measured oxygen tension, and throughout the investigation particular care was devoted to the measurement of this variable. For this reason, we used a dedicated electrode, insensitive to anaesthetic gases and operated by an experienced technician, in preference to an automated or semi-automated electrode system. As we have described in the methods section, a rigid calibration procedure was followed before and after every oxygen measurement and correction factors were applied to allow for electrode drift, blood:gas phase differences and elapsed time. Although samples were not taken into glass syringes, the plastic syringes were stored in iced water before use and returned there as soon as the sample had been taken. Decreases in $P\text{O}_2$ from this cause would have been greatest in the samples with the greatest values of $P\text{O}_2$, but are unlikely to have been greater than 1.5 kPa (Restall et al., 1975) because these samples were always analysed first. Corrections for differences in temperature between the patient and the electrode were not applied, since the calculation of content involves reconversion of $P\text{O}_2$ at the patient temperature back to a virtual $P\text{O}_2$ at 37 °C and it was felt that oxygen content would not change with temperature. Overall, in order to produce values of $\dot{Q}$va/$\dot{Q}$t at the highest $F\text{I}_{\text{O}_2}$ values similar to those obtained at $F\text{I}_{\text{O}_2}$ of about 50%, average $P\text{a}_{\text{O}_2}$ on nearly 100% oxygen would have needed to be more than 10 kPa greater than the corrected values.

The alveolar air equation used to calculate $P\text{A}_{\text{O}_2}$ was appropriate for use in the presence of nitrous oxide as it makes no assumptions about inert gas exchange (Nunn, 1977). Small errors in the calculation of $P\text{A}_{\text{O}_2}$ may have been introduced by a temperature difference between the alveoli and the assumed temperature of 37 °C, but these would have been minimal under the experimental conditions (Kerr, 1975). In this study, the effect of altering the $F\text{I}_{\text{O}_2}$ upon the calculation of $P\text{A}_{\text{O}_2}$ will differ depending upon the direction of change. When the $F\text{I}_{\text{O}_2}$ was increased (and the $F\text{I}_{\text{N}_2\text{O}}$, therefore, decreased), nitrous oxide would have continued to pass into the alveoli leading to an overestimate of $P\text{A}_{\text{O}_2}$ unless the Filley factor was applied. Only at the highest $F\text{I}_{\text{O}_2}$ was this not done, so that the resultant overestimate of $P\text{A}_{\text{O}_2}$ would lead to a slight underestimate of venous admixture at the highest value. After increases in $F\text{I}_{\text{N}_2\text{O}}$ the converse would apply, so that the net effect of reciprocal changes would have been an apparent reduction in the oxygen-dependent increase in venous admixture shown by most of our patients.

The suitability of central venous blood as a substitute for "true" mixed venous blood has been questioned (Dongre, McAslan and Shin, 1977). However, in those patients from whom we obtained paired samples, we were able to demonstrate a good correlation both between the absolute values of $\dot{Q}$va/$\dot{Q}$t and between the directions of change in $\dot{Q}$va/$\dot{Q}$t which subsequently occurred although, as others have found (Scheinman, Brown and Rapaport, 1969; Tahvanainen, Meretoja and Nikki, 1982), the use of caval blood led to a consistent overestimation of $\dot{Q}$va/$\dot{Q}$t. For these reasons, we do not consider it likely that the use of central venous blood for calculating $\dot{Q}$va/$\dot{Q}$t in those patients in whom pulmonary arterial blood was not available will have misrepresented the behaviour of their lungs when the $F\text{I}_{\text{O}_2}$ was changed, although it seems likely that the size of the changes was exaggerated.

We deliberately altered the sequence of exposure to the various $F\text{I}_{\text{O}_2}$ values from patient to patient for several reasons. First, we intended to minimize any possible time-dependent changes in $\dot{Q}$va/$\dot{Q}$t, notwithstanding the evidence that such changes appear not to occur (Dueck, Rathbun and Harrison, 1981). Second, we wished to expose the patients to both increasing and decreasing $F\text{I}_{\text{O}_2}$ in order to assess the reversibility (or otherwise) of any changes in venous admixture. Finally, by varying the exposure sequence, we hoped that any errors introduced by incomplete mixing during the equilibration period would be self-cancelling. In addition, this practice will have lessened any distortion in the pattern of response produced by our use of the initial haemoglobin concentration throughout the study. Although each 1-g decrease in haemoglobin concentration will cause the value of $\dot{Q}$va/$\dot{Q}$t derived from a given set of blood-gas measurements to be increased by a factor of about 1.05 (10 becomes 10.5% and 20 becomes 21%), changes were minimized in our patients by avoiding large crystalloid infusions and transfusing blood early, and by comparing $\dot{Q}$va/$\dot{Q}$t values at successive $F\text{I}_{\text{O}_2}$ values (table IV) rather than at widely spaced intervals during the operation. In designing the study we also sought to stabilize most of the suggested determinants of venous admixture and thereby isolate the effect of variations in the composition of the inspired gas. In particular, at each fractional concentration of oxygen, the lungs were ventilated at the same tidal volume, neither the cardiac output nor arterial pressure changed significantly and there was little change in either the mixed venous oxygen tension or the arterial $P\text{CO}_2$.

Physiology

The increases in $\dot{Q}$va/$\dot{Q}$t shown by several patients at the lower values of $F\text{I}_{\text{O}_2}$ are similar to those reported by other investigators (Douglas, Downs and Snook, 1980; Oliven, Abinader and Bursztein, 1980) and probably represent the passive effect of increasing unsaturation of blood from poorly ventilated lung units as the inspired and hence alveolar oxygen tensions decrease, rather than a change in true shunt. As $F\text{I}_{O_2}$ is reduced from about 40% towards 20%, the rate of increase of $\dot{Q}$va/$\dot{Q}$t resulting from a fixed amount of $\dot{V}/\dot{Q}$ mismatching accelerates so that any oxygen-dependent effect is likely to be obscured. In a study such as this it is not possible to distinguish between the effects of true shunt and those of low $\dot{V}/\dot{Q}$ units but, in a recent study using a multiple inert-gas elimination technique (Lundh and Hedenstierna, 1984), $\dot{V}$a/$\dot{Q}$ distributions remained unaltered when $F\text{I}_{O_2}$ was increased from about 30 to 50%.

It has recently been suggested (Dueck et al., 1980) that during nitrous oxide–oxygen anaesthesia the effects of poorly ventilated lung units on oxygen transfer may be camouflaged during ventilation with nitrous oxide in oxygen (60:40) mixtures because the $P\text{A}_{O_2}$ in such units may be increased by rapid N_2O uptake—a second-gas effect. While we accept that such a mechanism may increase Pa_{O_2} transiently, we find it difficult to conceive how enough oxygen can pass into what are, by definition, poorly ventilated alveoli in order to *sustain* a significant increase in arterial P_{O_2}. For this reason we do not believe that our estimates of venous admixture in the $F\text{I}_{O_2}$ range 0.3–0.5 were spuriously low.

Similarly, in view of the precautions taken with our measurements of oxygen tension, we feel confident in the accuracy of our determinations of venous admixture at the high $F\text{I}_{O_2}$ values and, thus, are driven to conclude that, in the presence of nitrous oxide, venous admixture often increases as $F\text{I}_{O_2}$ is increased in the range 0.5–0.99.

This pattern of response has in fact been observed previously during ventilation with nitrous oxide in oxygen mixtures (Michenfelder, Fowler and Theye, 1966; Bradshaw and Thompson, 1982) and is incompatible with that predicted by the "Critical $\dot{V}$a/$\dot{Q}$" hypothesis. (The latter suggests that, during ventilation with such mixtures, the tendency for poorly ventilated alveoli to collapse and hence to increase $\dot{Q}$va/$\dot{Q}$t would be largely independent of $F\text{I}_{O_2}$ (fig. 1).) This apparent contradiction can be considered in the light of at least four other observations which are also difficult to reconcile with "Critical $\dot{V}$a/$\dot{Q}$" as being an important mechanism for redistributing ventilation in the face of a changing $F\text{I}_{O_2}$:

(1) The increase in $\dot{Q}$va/$\dot{Q}$t observed when $F\text{I}_{O_2}$ is increased is readily reversed when $F\text{I}_{O_2}$ is decreased again, even when the pattern of ventilation is unchanged (McAslan et al., 1973; Kerr, 1975; Suter, Fairley and Schlobohm, 1975; Reines and Civetta, 1979; Quan et al., 1980; Lundh and Hedenstierna, 1984). This observation, reconfirmed in the present study, requires that lung units, which according to the "Critical $\dot{V}$a/$\dot{Q}$" theory should have become atelectatic in order to contribute to the increased shunting at high $F\text{I}_{O_2}$, re-open within a short time (15–30 min) of exposure to a lower $F\text{I}_{O_2}$. In view of this rapid reversibility, it could be argued that the subcritical units remained open by inspiring alveolar gas from neighbouring units during the expiratory phase of the rest of the lung ("collateral ventilation") (Dantzker, Wagner and West, 1975). This appears unlikely as, under these conditions, the lung unit should remain effective for oxygen uptake but ineffective for carbon dioxide elimination and thus should not be detected as venous admixture by our measurements.

(2) It might be expected that alveolar atelectasis of the degree required to produce the observed increases in $\dot{Q}$va/$\dot{Q}$t would be accompanied by detectable reductions in lung volume. However, Suter, Fairley and Schlobohm (1975) failed to demonstrate a progressive decrease in lung volume in spite of steadily increasing $\dot{Q}$va/$\dot{Q}$t as $F\text{I}_{O_2}$ was increased to 90%, although there was a decrease in functional residual capacity (FRC) after ventilation with 100% oxygen. Conversely, Heneghan, Bergman and Jones (1984) were unable to initiate changes in oxygenating efficiency during anaesthesia by altering FRC. Thus, it would appear that significant changes in $\dot{Q}$va/$\dot{Q}$t can occur independently of changes in lung volume.

(3) In most of the studies reported, insufficient time has been allowed after $F\text{I}_{O_2}$ changes to permit atelectasis to occur. McAslan and colleagues (1973) found increases in $\dot{Q}$va/$\dot{Q}$t after 5 min ventilation with 100% oxygen and in most of the other studies equilibration times of between 15 and 30 min have been used. In the absence of N_2O, the critical $\dot{V}$a/$\dot{Q}$ theory predicts that considerably longer time periods would be necessary for alveolar collapse to take place, particularly at the intermediate values of $F\text{I}_{O_2}$.

(4) In most of their patients, Lundh and Hedenstierna (1984) found increasing true shunt as $F\text{I}_{O_2}$ was increased from 53 to 85% without demonstrating the presence of lung units with $\dot{V}$a/$\dot{Q}$ ratios in the "critical" range. In one of

their nine patients such units were found, and it appeared that they became atelectatic on ventilation with 85% oxygen and remained so on return to a lower FI_{O_2}.

Since it seems unlikely that, in most patients, the oxygen-dependent increase in Qva/Qt can be explained by a passive redistribution of ventilation based on the physical properties of the respiratory gases, an alternative possibility, that of an oxygen-mediated redistribution of the pulmonary blood flow, must be considered as the main cause of this phenomenon. This conclusion has been reached by other investigators (Kerr, 1975; Suter, Fairley and Schlobohm, 1975; Lundh and Hedenstierna, 1984) and is strongly reinforced by the results of this study. The mechanism of the redistribution remains unclear, however, since, unlike pulmonary hypoxic vasoconstriction in man (Bjertnaes, 1978), it occurs in the presence of halothane (Michenfelder, Fowler and Theye, 1966; Drummond, Wildsmith and Masson, 1978; Lundh and Hedenstierna, 1984), and there is no obvious relationship between the change in Qva/Qt and changes in mixed venous oxygenation.

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PULMONARY GAS EXCHANGE AND DIAPHRAGMATIC POSITION

Effect of Tonic Phrenic Stimulation Compared with that of Increased Airway Pressure

C. P. H. HENEGHAN AND J. G. JONES

The impairment of pulmonary gas exchange observed in man during anaesthesia has been correlated significantly with the decrease in lung volume which occurs simultaneously (Hickey et al., 1973; Hewlett et al., 1974). In spite of this, gas exchange is not improved significantly by returning lung volume to its pre-anaesthetic values (Wyche et al., 1973; Heneghan, Bergman and Jones, 1984), an observation which could be seen to disprove the hypothesis that the impairment in gas exchange is causally related to the decrease in lung volume. Alternatively, the abnormality in gas exchange could be caused by a change in the shape and position of the diaphragm as a result of the effects of anaesthesia on the phasic and tonic activity of the respiratory muscles (Jones, 1977). In this case, the decrease in lung volume is a manifestation of this change, but the restoration of lung volume to pre-anaesthetic values may not restore diaphragmatic position, regional lung volume, regional lung recoil pressure, or normal regional ventilation. This theory is supported by the observation that, in supine man, anaesthesia alters diaphragmatic tone and movement, with a cephalad displacement of, and reduction of movement in, the dependent, dorsal part of the diaphragm (Froese and Bryan, 1974). Furthermore, during positive pressure ventilation, the greatest diaphragmatic excursion is shifted from the dependent, dorsal part to the upper, ventral part. This is believed to decrease the ventilation in the dependent part of the lung and worsen the matching of ventilation to perfusion, thus producing the abnormality of gas exchange associated with the induction of anaesthesia.

SUMMARY

The influence of diaphragmatic position on abnormal gas exchange has been examined to investigate the theory that the impairment in gas exchange in anaesthetized man is caused by disturbance of diaphragmatic mechanics, resulting in abnormalities of dependent lung ventilation. A gas exchange abnormality, probably caused by airway closure in the dependent regions of the lung, was induced in anaesthetized rabbits by reducing lung volume to residual volume and allowing passive re-expansion. The effects on gas exchange of increases in lung volume produced by two methods—the application of positive end-expiratory pressure (PEEP) and phrenic nerve stimulation (PNS)—were compared. Both methods were adjusted to give the same increase in lung volume. PNS was found to produce greater caudal movement of the diaphragm than PEEP, particularly in the dependent regions. PNS also improved gas exchange significantly more than PEEP. These findings support the theory that alterations in diaphragmatic mechanics during anaesthesia contribute to the gas exchange impairment in man.

The present study was designed to test this theory. The ideal approach would have been to restore tone and movement to the diaphragm, so as to regain the position and pattern seen in the awake state. However, no method has been devised to achieve this in anaesthetized animals or man. Therefore we adopted a different approach in an animal model and, after inducing an abnormal gas exchange in the dependent part of the lung, increased lung volume in two ways, one passive and one active, ensuring that the change in

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lung volume was the same under both conditions. The two ways were, first, by increasing end-expiratory airway pressure and, second, by tonic stimulation of the phrenic nerves. The former was expected to displace the diaphragm predominantly in the upper, ventral part, analogous to the findings of Froese and Bryan (1974). The latter was expected to produce movement predominantly in the dependent, dorsal part. In this way, the same increase in lung volume—produced by movement of different parts of the diaphragm—would be expected to have different effects on the induced abnormality of gas exchange.

MATERIALS AND METHODS

Arterial and venous cannulae were inserted under local anaesthesia to ear vessels of five 3-kg sandy halflop rabbits and samples of arterial blood (control) were taken. All samples were drawn into heparinized 2-ml glass syringes and blood-gas analysis was carried out immediately on an IL 613 blood-gas analyser calibrated before each measurement.

Each rabbit was then anaesthetized with a fentanyl–diflunisal mixture (Hypnorm) 0.5 ml i.m. and diazepam 2.5 mg i.v. Supplementary doses of Hypnorm 0.1 ml and diazepam 1.0 mg were administered as indicated clinically. The rabbit was turned supine and remained in this position throughout the remainder of the experiment. The trachea was dissected free, and a tracheostomy tube was introduced. The lungs were ventilated mechanically with air using a Harvard small animal respirator, giving a tidal volume of 20 ml. Ventilatory frequency was adjusted to produce normocapnia. Arterial pressure and airway pressure were recorded continuously with strain gauges and displayed on a chart recorder, and tidal flow was measured using a pneumotachograph with tidal volume derived by electronic integration.

The phrenic nerves were dissected free bilaterally. The cervical nerve roots were exposed and a leash of nerves was seen to deviate caudally from the main stream. This was demonstrated by electrical stimulation to contain a mixture of fibres which moved the forequarter and others which moved the diaphragm. Further blunt dissection allowed the more medial fibres, leading to the diaphragm, to be separated from those to the forequarter, and a cotton thread to be looped around the fibres supplying the diaphragm. Once separated, these fibres made up a bundle of about 0.5 mm in diameter: this will henceforth be referred to as the phrenic nerve.

After bilateral dissection, each nerve was laid across a set of fine wire electrodes from a bipolar nerve stimulator and covered with a saline-soaked swab. The stimulating voltage was adjusted so that the increase in lung volume, measured by integration of the pneumotachograph signal, was 20 ml, the same as the tidal volume. The stimulating frequency was 20 Hz, which produced the best balance between contractile force and rate of fatigue (Edwards, 1978). At this point, radiographic screening was used to confirm that bilateral diaphragmatic movement was occurring, and the screening was repeated each time phrenic nerve stimulation (PNS) was instituted.

Positive end-expiratory pressure (PEEP) was adjusted to increase the FRC to the same volume as with PNS, that is, 20 ml. Cine-radiographs were taken to record the position and movement of the diaphragm in control conditions, and during PNS and PEEP.

Functional residual capacity (FRC) was measured by helium dilution: a 20-ml syringe containing 10% helium in air was attached to the airway (at end-expiration) via a side arm in the ventilator circuit and the lungs were ventilated with the syringe for six to eight breaths. Helium concentration was later measured by mass spectrometry.

Impairment of gas exchange was induced by applying a syringe to the airway and applying a subatmospheric pressure of 30 cm H_2O; this resulted in the lungs being emptied to residual volume (RV). In a previous study this manoeuvre had been observed to produce a sustained reduction in pulmonary compliance—as shown by an increase in airway pressure.

After the induction of anaesthesia and bilateral phrenic dissection, two studies were performed, the first in four rabbits, the second in five. In the four rabbits in which both studies were performed, the order was randomized.

Study 1. To test the effects of PEEP and PNS in the absence of any prior intervention

A control series of measurements was obtained. This consisted of taking an arterial blood sample and measuring the blood-gas tensions, measuring FRC, and running the recorder at a fast rate to record dynamic airway pressure and flow traces for the subsequent measurement of tidal volume, end-inspiratory and end-expiratory pressure, and dynamic compliance (C_{dyn}). C_{dyn} was calculated as the tidal volume divided by the corresponding pressure change, with both measured at points of zero flow. FRC was then increased by either PEEP or PNS, the order being randomized. The series of measurements was repeated and the FRC was then allowed to return to control. The whole procedure was repeated in the same animal, once the FRC had been increased by the other method.

Study 2. To test the effects of PEEP and PNS after induction of a gas exchange abnormality

This experiment was a repeat of that described above, but modified to create an abnormality of gas exchange by decreasing the volume of the lungs to RV by the application of a subatmospheric pressure of 30 cm H_2O, and then allowing the lungs to inflate passively. This will be referred to as "the RV manoeuvre". Thus, the procedure had four extra steps: the RV manoeuvre at the beginning of each half of the investigation, and reinflation with a triple tidal volume at the end of each half. This means that there were nine steps in total: control, the RV manoeuvre, PEEP (or PNS) on, PEEP (or PNS) off, reinflation, the RV manoeuvre, PNS (or PEEP) on, PNS (or PEEP) off, reinflation. A complete series of measurements (as above) was performed at each of these nine steps.

Alveolar–arterial oxygen tension difference ($P_{A_{O_2}} - Pa_{O_2}$) was calculated using the equation:

$$P_{A_{O_2}} = P_{I_{O_2}} - Pa_{CO_2}/R + F_{I_{O_2}} \cdot Pa_{CO_2} \cdot (1-R)/R$$

where the Pappenheimer convention is used throughout, and R = respiratory exchange ratio, which was assumed to be 0.8. Eleven 1-ml blood samples were taken from each animal. Each sample was replaced by an equal volume of Ringer's lactate solution.

Statistical analysis

Comparison of data was by two-way analysis of variance, unless otherwise stated.

RESULTS

In every rabbit there was a decrease in ($P_{A_{O_2}} - Pa_{O_2}$) with the induction of anaesthesia, and Pa_{O_2} was increased: the change was statistically significant (table I).

TABLE I. *Blood-gas tensions and alveolar–arterial oxygen tension difference in awake and anaesthetized rabbits. Awake: spontaneously breathing air,* not *sedated. Anaesthetized: IPPV with air, zero end expiratory pressure, Hypnorm and diazepam anaesthesia.* $P < 0.01$, *paired* t-*test*

	Awake			Anaesthetized		
	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	($P_{A_{O_2}} - Pa_{O_2}$) (kPa)	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	($P_{A_{O_2}} - Pa_{O_2}$) (kPa)
	12.1	3.9	3.1	14.0	4.2	0.8
	11.4	3.7	4.0	14.2	4.2	0.6
	10.5	5.0	3.4	11.1	5.0	2.8
	10.9	4.7	3.4	13.3	5.0	0.6
	9.2	4.4	5.4	12.1	4.4	2.5
	9.5	4.9	4.5	12.2	3.8	3.1
Mean			4.0			1.7
SD			0.9			1.2

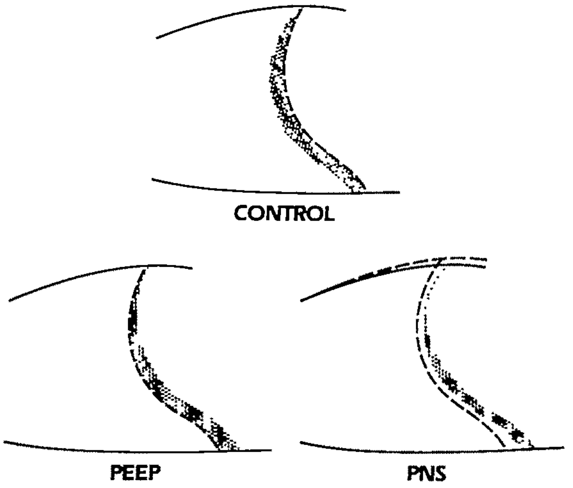

FIG. 1. Tracings from lateral cine-radiographs, showing diaphragmatic position and motion in three conditions: Control, during phrenic stimulation (PNS), and with increased airway pressure (PEEP). Dotted line = control end-*in*spiratory position; shaded area = diaphragmatic tidal excursion.

Position and motion of the diaphragm

The effects of PEEP and PNS on the position and motion of the diaphragm are illustrated in figure 1, and in table II the displacements of different parts of the diaphragm which resulted from the two interventions in three animals are shown. PNS produced more movement of the diaphragm throughout its length, and this difference was statistically significant in the dorsal section.

TABLE II. *Mean movement of the diaphragm caudally (mm) (SEM) resulting from PNS and PEEP.* n = *3. Measurements made from tracings of lateral cine-radiographs: "ventral" = 1 cm posterior to the most anterior point of diaphragm; "middle" = midpoint of antero-posterior diameter of thorax measured from vertebral body to xiphisternum, "dorsal" = 1 cm anterior to the most posterior point of diaphragm.* *P < *0.05*

	PNS	PEEP
Ventral	7.3 (0.3)	5 (0)
Middle	12.3 (2.3)	10.7 (0.9)
Dorsal	18.7 (6.2)	9.7 (0.7)*

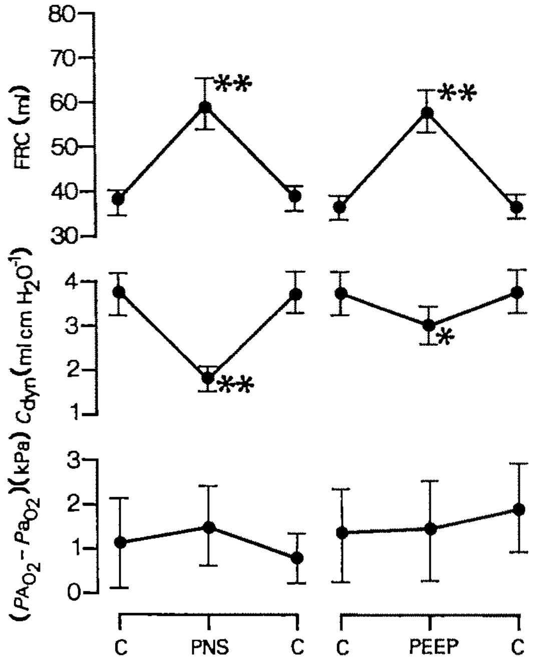

FIG. 2. Investigation 1: The effect of PNS and PEEP on FRC, C_{dyn} and ($P\text{A}_{O_2} - P\text{a}_{O_2}$). Values are mean and SEM. **$P < 0.01$, *$P < 0.05$, compared with controls.

Study 1

FRC, C_{dyn} and ($P\text{A}_{O_2} - P\text{a}_{O_2}$) at each step of the experiment are shown in figure 2. There were significant changes of both FRC and C_{dyn} with both PEEP and PNS, with no change in ($P\text{A}_{O_2} - P\text{a}_{O_2}$).

Study 2

The position and motion of the diaphragm were unaffected by the RV manoeuvre. In both halves of the experiment, this produced a consistent, significant decrease in C_{dyn} (fig. 3B), with no change in FRC (fig. 3A), and a consistent,

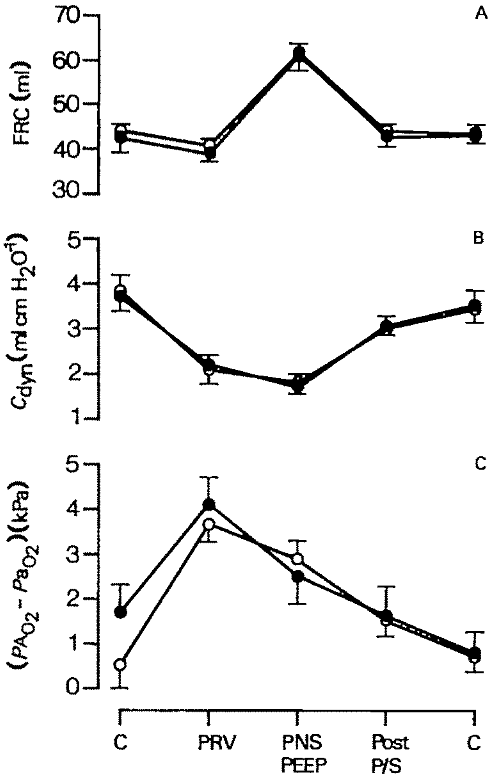

FIG. 3. Study 2 (mean and SEM). C = Control; PRV = post residual volume (after application of subatmospheric pressure of 30 cm H_2O to airway, reducing lung volume to residual volume); PNS/PEEP = during application of the relevant intervention; Post P/S = immediately after PNS or PEEP. ● = PNS; ○ = PEEP. *Statistics:* There were no differences between PNS and PEEP data, absolute values. A: Decrease in FRC in PRV group was not significant ($0.1 > P > 0.05$), returning to control in post P/S. B: PRV and PNS/PEEP different from all other values ($P < 0.001$), and PRV different from PNS and PEEP ($P < 0.01$). C: Each value in both runs different from previous value ($P < 0.05$); PRV *v.* C, PNS *v.* PRV, $P < 0.001$; PEEP *v.* PRV, $P = 0.04$).

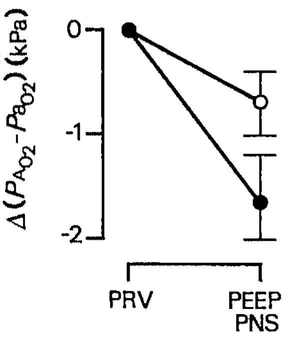

FIG. 4. Comparison of change of ($P\text{A}_{O_2} - P\text{a}_{O_2}$), PRV to PNS and PRV to PEEP. Symbols as for figure 3. $P = 0.02$.

significant increase in $(P\text{A}_{O_2}-P\text{a}_{O_2})$ (fig. 3C). The introduction of both PNS and PEEP improved gas exchange, but the improvement with PNS was significantly greater than that with PEEP (fig. 4). There was partial recovery of compliance and gas exchange after discontinuation of both PNS and PEEP, and there was no difference between the two halves of the investigation at this stage. After a three tidal volume hyperinflation manoeuvre, gas exchange recovered to control values (fig. 3C).

Although the efficiency of gas exchange was slightly worse (i.e. slightly higher $(P\text{A}_{O_2}-P\text{a}_{O_2})$) overall in association with PNS (fig. 3C), gas exchange was better with PNS than with PEEP.

In the four animals in which arterial pressure recordings were technically adequate, there was a slightly greater decrease in mean arterial pressure during PNS (9.8 mm Hg, SEM 4.8) than during PEEP (6.2 mm Hg, SEM 4.4). This difference was not significant ($P > 0.05$), and there was no correlation between change in arterial pressure and change in $(P\text{A}_{O_2}-P\text{a}_{O_2})$ ($P = 0.8$ by regression analysis).

DISCUSSION

There are five interesting findings in this study:

(a) Gas exchange, far from being impaired, was actually improved by the induction of anaesthesia and the supine posture in the rabbit.

(b) Neither PEEP nor PNS had any consistent effect on $(P\text{A}_{O_2}-P\text{a}_{O_2})$ if no gas exchange abnormality had been induced.

(c) There was no significant change in FRC when C_{dyn} was decreased substantially (and $(P\text{A}_{O_2}-P\text{a}_{O_2})$ considerably increased) by the RV manoeuvre.

(d) After the RV manoeuvre, PNS improved $(P\text{A}_{O_2}-P\text{a}_{O_2})$ significantly more than PEEP.

(e) Diaphragmatic position was affected differently by PEEP and PNS, and, unlike in man (Froese and Bryan, 1974), movement of the diaphragm was greater in the dependent than in the upper portion in both conditions.

The failure of anaesthesia to produce a gas exchange abnormality in the rabbit means that this model is not directly comparable to the human. The reason for this difference is obscure, but may be related to the difference in diaphragmatic movement in the rabbit, producing better ventilation in the dependent parts of the lung. The absence of impairment in gas exchange led us to use the technique of inducing one by a transient reduction of lung volume to RV, and to investigate the effects of PEEP and PNS on this induced impairment. Clearly, this model may not be a precise analogue of the impairment in gas exchange induced by anaesthesia in man; however, there is compelling evidence that the RV manoeuvre induces changes predominantly in the dependent parts of the lung (Jones, 1982), so the likelihood is considerable that this is a close analogue. Second, even if this is not a closely analogous model, it does represent a model of impairment in gas exchange which is quantitatively comparable to that induced by anaesthesia in man and is, thus, a useful tool with which to investigate factors which may affect gas exchange.

The lack of any effect of PEEP or PNS on $(P\text{A}_{O_2}-P\text{a}_{O_2})$ in the first investigation is not very surprising, as there was no impairment of gas exchange and, thus, probably little maldistribution of ventilation, and little scope for improvement. Neither PEEP nor PNS worsened $(P\text{A}_{O_2}-P\text{a}_{O_2})$, so if either intervention decreased venous return and cardiac output, this did not decrease $P\bar{\text{v}}_{O_2}$ sufficiently to increase $(P\text{A}_{O_2}-P\text{a}_{O_2})$.

The observation that one can induce a major reduction in pulmonary compliance and produce a significant increase in $(P\text{A}_{O_2}-P\text{a}_{O_2})$ without affecting FRC significantly is difficult to interpret. The obvious mechanism for the reduced C_{dyn} following the RV manoeuvre is airway closure (Jones, 1982), and the impairment of gas exchange would then be caused by the regional hypoventilation resulting from this. However, in spite of a major reduction in compliance, which should represent closure of a large proportion of the airways, FRC was not decreased, when measured either by helium dilution, or radiographically. This could be explained by measurement errors, but these are unlikely, since the increases in FRC induced by PEEP and PNS were easily detected with helium dilution and radiographically. The only other explanation which fits the data is that reducing lung volume to RV results in a greater non-linearity of the lung compliance curve than in the normal state, so that the recoil pressure at FRC is the same as at the control FRC, but above this volume the recoil pressure is considerably greater.

Next there is the observation that PNS improved $(P\text{A}_{O_2}-P\text{a}_{O_2})$ more than did PEEP. Lateral radiography revealed that, during PNS, the dorsal part of the diaphragm was more caudal at end-expiration and would, thus, exert a greater distending force on the dependent lung than during PEEP. PNS would, therefore, tend to open airways more than PEEP so that, although tidal diaphragmatic motion was similar in PNS and PEEP, regional ventilation would be better during PNS. The greater concurrent improvement in $(PA_{O_2}-Pa_{O_2})$ during PNS supports the idea that regional ventilatory abnormalities, like the changes seen by Froese and Bryan (1974), contribute to the impairment in gas exchange seen during anaesthesia in man.

It is possible that this finding results from different changes in cardiac output during PEEP and PNS: although PEEP and PNS both increase airway pressure, PEEP increases airway pressure throughout the respiratory cycle, whereas PNS only increases the inspiratory pressure, leaving expiratory pressure at zero. If cardiac output were significantly differentially affected, this might be reflected in changes in arterial pressure. Although there was a tendency for arterial pressure to be decreased more by PNS, this did not reach statistical significance, nor was there a correlation between the change in mean arterial pressure and $(PA_{O_2}-Pa_{O_2})$. Under these circumstances, it is unlikely that this mechanism is important in generating the difference between PEEP and PNS.

It is interesting to note that the motion of the rabbit diaphragm in response to the two manoeuvres was not as expected from the work of Froese and Bryan (1974). They showed that, during anaesthesia in man, mechanical ventilation moved the *anterior* part of the diaphragm more, while spontaneous ventilation moved the *posterior* part more. Therefore we expected that PEEP would affect mainly the ventral part of the diaphragm of the rabbit and PNS the dorsal part. In fact, we observed that there was always a greater movement in the *dorsal* part of the diaphragm, and a gradient of motion from ventral to dorsal. This difference from man was quite unexpected, and it may arise from the difference in the shape of the rabbit chest wall and diaphragm, and the stresses imposed on them by the abdominal contents. Thus in man, the chest can be described as having a modified oval cross section, while that of the rabbit, like many quadrupeds, is much more triangular, pointed ventrally. This would tend to reduce the freedom of movement of the ventral part of the diaphragm, since it is tethered laterally much more than that of man.

In conclusion, we have investigated whether two different methods of increasing lung volume during anaesthesia, increasing airway pressure and phrenic nerve stimulation, have different effects on pulmonary gas exchange. Phrenic stimulation improved $(PA_{O_2}-Pa_{O_2})$ more than PEEP did, which supports the theory that abnormalities of gas exchange observed during anaesthesia may be attributable to regional alterations in chest wall motion.

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COMPARISON OF PROPOFOL WITH METHOHEXITONE IN THE PROVISION OF ANAESTHESIA FOR SURGERY UNDER REGIONAL BLOCKADE

N. MACKENZIE AND I. S. GRANT

SUMMARY

Propofol was compared with methohexitone for provision of light general anaesthesia in patients undergoing surgery under spinal analgesia. Intermittent bolus administration of both agents proved a feasible way of maintaining anaesthesia, a mean infusion rate of 0.13 mg kg^{-1} min^{-1} being required for propofol and 0.089 mg kg^{-1} min^{-1} for methohexitone. Propofol produced smoother anaesthesia with significantly fewer excitatory side effects and less pain on injection, but cardiovascular and respiratory depression occurred commonly. Recovery was rapid with both agents, but minor postoperative sequelae occurred more frequently after methohexitone.

Di-isopropyl phenol is a recent addition to the range of i.v. induction agents, its use first being described by Kay and Rolly in 1977. Initial studies suggested it would be a satisfactory agent for continuous infusion or repeated bolus administration, since it is rapidly metabolized with little evidence of cumulation and recovery is rapid, with relative freedom from side effects (Rogers et al., 1980; Rutter et al., 1980; O'Callaghan et al., 1982). However, these advantages were largely outweighed by formulation in Cremophor EL, which is implicated in hypersensitivity reactions (Briggs, Clarke and Watkins, 1982; Glen, Hunter and Thomson, 1982), and by the high incidence of pain on injection.

An alternative formulation has now been achieved with a 1% w/v aqueous emulsion containing 10% w/v soya bean oil, 1.2% w/v egg phosphatide and 2.3% w/v glycerol. Initial animal studies showed that this has anaesthetic properties generally similar to those of the Cremophor formulation (Glen and Hunter, 1984). The purpose of this study was to compare the emulsion formulation, propofol, with methohexitone for the induction and maintenance of light general anaesthesia in patients undergoing surgery under regional analgesia, with particular regard to postoperative recovery.

METHODS

Forty patients aged between 16 and 65 yr, undergoing orthopaedic surgery on the lower limbs under regional analgesia, were allocated randomly to one of two groups of 20 receiving either propofol or methohexitone. All were ASA grade 1 or 2 and those with hepatic, renal, haematological, metabolic or psychiatric disease were excluded. Informed consent was obtained from each patient and the study was approved by the Hospital Ethical Committee.

Before operation each patient was instructed in the use of the Leeds Psychomotor Tester. This is a compact, portable apparatus capable of measuring Critical Flicker Fusion Threshold (CFFT) and Choice Reaction Time (CRT) (Hindmarch and Parrott, 1977). Taken together, these assessments gave accurate, reproducible information on the effects of psychoactive drugs on normal central nervous system function (Hindmarch, 1980).

For CRT measurement the subject scans an array of six small lights which are illuminated on a random basis. As soon as he detects the light he touches the appropriate button to extinguish it. The latency of this response provides a good assessment of the integrity of sensori-motor function. The distance the subject has to move his hand to touch the response button is the same for

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each light, making it possible to measure motor time separately from recognition time.

The CFFT is a sensitive index of the state of CNS arousal and the ability to integrate discrete units of sensory data. In this assessment the subject is required to detect flicker fusion in a set of four light-emitting diodes in foveal fixation at 1 m, responding to alternately ascending and descending frequencies.

After familiarization with the apparatus, each subject had 50 practice attempts with the CRT component before a preoperative base-line CFFT and CRT score was recorded. This is recommended by the designers to preclude any possible learning effect interfering with assessment of performance. The CRT was taken as the mean of 25 response times following five practice attempts on each occasion and the CFFT as the mean of six results, three on the ascending scale and three on the descending. For every subject, care was taken to ensure correct positioning of the apparatus and a constant level of ambient lighting.

No premedication was given and, on arrival of the patient in the anaesthetic room, Hartmann's solution was infused i.v. via a peripheral vein on the dorsum of the hand. Arterial pressure and heart rate were recorded and spinal anaesthesia instituted with an intrathecal injection of 2.5 or 3 ml of 0.75% bupivacaine plain via a 25-gauge needle in the lumbar region.

The patients received either propofol 2.5 mg kg^{-1} or methohexitone 1.5 mg kg^{-1} over a 20-s period via the venous cannula, to induce general anaesthesia. The induction time (time from start of injection to cessation of counting) was noted, as were any complications during induction such as feelings on injection, movement, apnoea and other respiratory problems. The overall quality of induction was graded by the anaesthetist. Light general anaesthesia was maintained by repeated bolus injections of approximately one-quarter to one-third of the induction dose, using the eyelash reflex as a clinical indicator of depth of anaesthesia. All patients breathed oxygen 4 litre min^{-1} through a Hudson mask and no other drugs were given. Circulating blood volume was maintained with Hartmann's solution or whole blood where appropriate. Heart rate and arterial pressure were recorded 2 min after induction and at 5-min intervals thereafter. Any excitatory or other unwanted side effects during the maintenance period were recorded and the overall quality of anaesthesia graded.

At the end of surgery two recovery times were noted, both from the last dose of anaesthetic agent: time to open eyes on command and time to recall date of birth. The patient was then transferred back to the ward, where recovery was further assessed by CFFT and CRT measurement at 30, 60, 120 and 240 min from awakening. This was carried out by a second anaesthetist who was unaware of the anaesthetic received by the patient. Any adverse effects during the recovery period, such as headache, nausea, vomiting and restlessness, were noted at these times and again 24 h later. The regional block provided sufficient analgesia after operation to avoid the need for additional analgesia during the period of psychometric testing. The vein used for injection was inspected immediately after operation and again 24–72 h later, for any evidence of thrombosis or phlebitis.

A further control group of 20 patients not undergoing surgery and matched for age, sex and weight also underwent psychometric testing under conditions identical to those experienced by the study group. These patients had not undergone surgery within 5 days of the testing and were not taking any psychoactive drugs.

The results were analysed statistically using Student's *t* tests, chi-squared tests and Fisher's exact tests where appropriate.

RESULTS

All the groups (propofol, methohexitone and control) were comparable for age, sex and weight (table I).

Anaesthesia was successfully induced in all patients with a single bolus dose of anaesthetic agent, the mean induction time for both agents being approximately 30 s (table II). However, induction complications varied significantly between the two groups. Feelings on injection occurred in eight patients receiving propofol compared with 12 receiving methohexitone and in the latter group significantly more described these as painful. Excitatory effects during induction,

TABLE I. *Patient data (mean ± SEM)*

	Propofol	Methohexitone	Control
Age (yr)	39.3±3.23	38.7±3.79	41.2±3.22
Weight (kg)	69.7±3.46	71.9±2.81	68.6±2.16
Sex			
Male	13	15	14
Female	7	5	6

TABLE II. *Induction times (mean ± SEM) and complications (No. of patients).* **$P < 0.01$

	Propofol		Methohexitone
Induction time (s)	30.8 ± 1.27		31.7 ± 1.48
Apnoea			
Nil	5		12
<30 s	2		4
30–60 s	9		2
>60 s	4	**	2
Side effects			
Feelings on injection	8		12
Pain on injection	1	**	9
Excitatory effects	4	**	15

TABLE III. *Duration of anaesthesia (mean ± SEM), mean infusion rate (mean ± SEM) and complications during maintenance (No. of patients).* **$P < 0.01$

	Propofol		Methohexitone
Duration of anaesthesia (min)	51.6 ± 8.39		58.7 ± 5.39
Mean administration rate (mg kg^{-1} min^{-1})	0.130 ± 0.012		0.089 ± 0.007
Complications			
Excitatory effects	3	**	12
Cough	2		6
Airway obstruction	3		5
Apnoea (0–30 s)	3		1
Awareness	1		2

such as spontaneous movement, twitching, tremor and hiccup, were also significantly more frequent with methohexitone, occurring in 75% of patients compared with only 20% after propofol.

Apnoea following induction was seen significantly more often with propofol. Twice as many patients (15) developed apnoea with a mean duration of 63 s, compared with methohexitone (8), with which the mean duration was 45 s.

Duration of anaesthesia was similar in both groups, being just less than 1 h (table III). A mean administration rate for each agent was calculated by dividing the total dose of drug given (including the induction bolus) by the duration of anaesthesia, giving 0.13 mg kg^{-1} min^{-1} for propofol and 0.089 mg kg^{-1} min^{-1} for methohexitone.

Minor complications during anaesthesia, such as cough and airway obstruction, occurred more frequently with methohexitone and significantly more patients in this group exhibited excitatory effects such as spontaneous movement, twitching, hypertonus and hiccup. Awareness was reported in one patient receiving propofol and two receiving methohexitone, but it must be noted that general anaesthesia was being maintained intentionally at a light level on the background of regional nerve blockade.

Significant differences in cardiovascular variables occurred between the two groups (fig. 1). Mean arterial pressure decreased by approximately 10 mm Hg 2 min after injection of propofol, compared with a mean increase of approximately 3 mm Hg after methohexitone. Throughout maintenance with propofol, arterial pressure remained significantly below baseline values, whereas it changed little with methohexitone. In contrast, propofol produced little change in heart rate 2 min after induction, while methohexitone increased it by approximately 16 beat min^{-1}. This tachycardia persisted during the early maintenance period. In both groups heart rate decreased slightly during the procedure and significant differences were seen only in the first 10 min.

No significant differences in the early indices of recovery were found between the two groups (table IV). For both agents, the times from last dose to opening eyes on command and repeating date of birth were approximately 9 min.

Minor postoperative sequelae were rare following propofol, only one patient experiencing headache and nausea during early recovery. By contrast, six patients in the methohexitone group suffered side effects and in two patients these persisted for 24 h. No venous sequelae such as thrombosis or phlebitis were seen in either group in the early recovery period or at subsequent examination 24–72 h later.

TABLE IV. *Crude recovery times (mean ± SEM) and postoperative sequelae (No. of patients)*

	Propofol	Methohexitone
Time from last dose to end of surgery (min)	8.4 ± 0.95	8.1 ± 0.95
Time from last dose to open eyes (min)	9.3 ± 0.94	8.8 ± 0.92
Time from last dose to repeat DOB (min)	9.3 ± 0.89	9.1 ± 0.87
Postoperative sequelae		
Headache		
Early	1	5
24 h	0	2
Nausea + vomiting		
Early	1	5
24 h	0	2
Restlessness + confusion	0	2

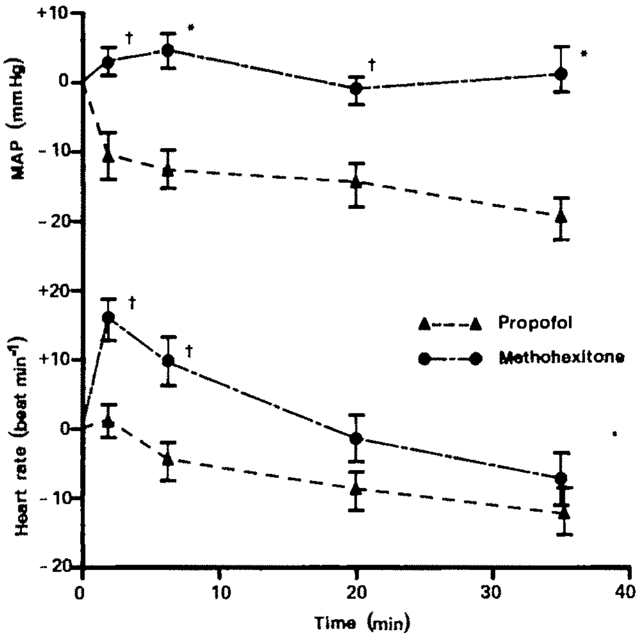

FIG. 1. Mean (±SEM) changes in arterial pressure and heart rate. Significant differences between propofol and methohexitone: $^*P < 0.001$; $^\dagger P < 0.01$.

Overall assessment of anaesthesia and recovery was made for each patient, induction and maintenance by the anaesthetist and recovery by an independent assessor. In all respects, propofol appeared superior to methohexitone (table V).

The results of the psychometric studies are displayed graphically in figures 2–5. Both agents depressed the Critical Flicker Fusion Threshold in a similar manner. With propofol this was significant at all times, but with methohexitone it was no longer significant after 4 h. Generally similar impairment of Choice Reaction Times also was seen with the two groups. After propofol, both elements of CRT were significantly impaired at 30 min, but only the motor component at 60 min. With methohexitone all measures were significantly impaired at 30 and 60 min. With neither agent were there significant effects at 2 and 4 h. No significant changes were apparent in CFFT or CRT over the 4-h assessment period in the control group.

TABLE V. *Quality of induction, maintenance and recovery (No. of patients)*

	Propofol	Methohexitone
Quality of induction		
Good	17	11
Adequate	3	7
Poor	0	2
Quality of maintenance		
Good	17	12
Adequate	3	7
Poor	0	1
Quality of recovery		
Good	19	17
Adequate	1	3
Poor	0	0

DISCUSSION

We have shown that propofol is a suitable agent for induction and maintenance of light general anaesthesia in patients undergoing surgery under regional blockade. It produced rapid, smooth induction, satisfactory anaesthetic maintenance and rapid postoperative recovery. Compared with methohexitone, there was little pain on injection, infrequent excitatory and other side effects and minimal postoperative sequelae. There was, however, considerably more cardiovascular and respiratory depression with propofol, although at no time was this clinically important.

The decreases in arterial pressure were within

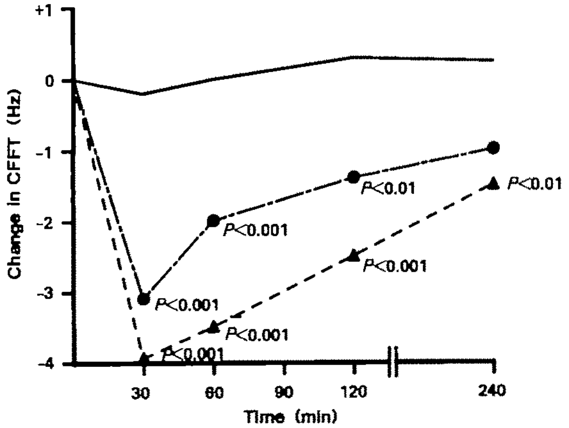

FIG. 2. Mean changes from pre-test baselines of CFFT. —— = Control; ▲ = propofol; ● = methohexitone.

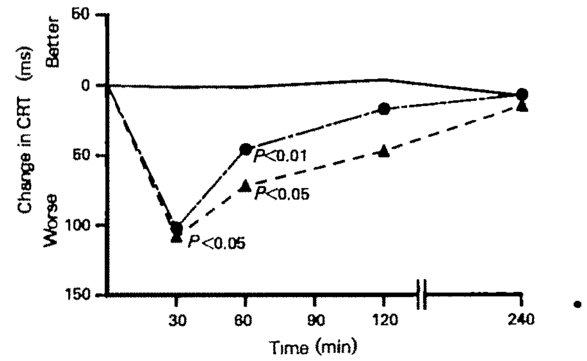

FIG. 4. Mean changes from pre-test baselines of motor component of CRT. —— = Control; ▲ = propofol; ● = methohexitone.

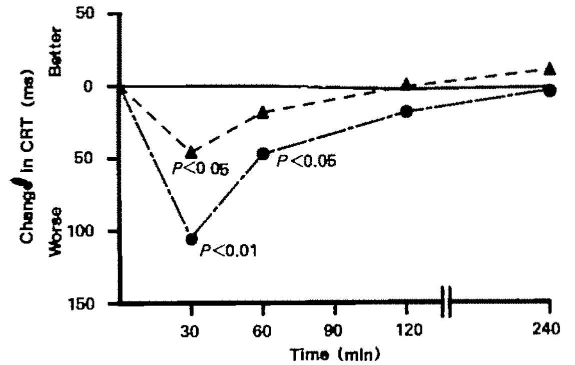

FIG. 3. Mean changes from pre-test baselines of recognition component of CRT. —— = Control; ▲ = propofol; ● = methohexitone.

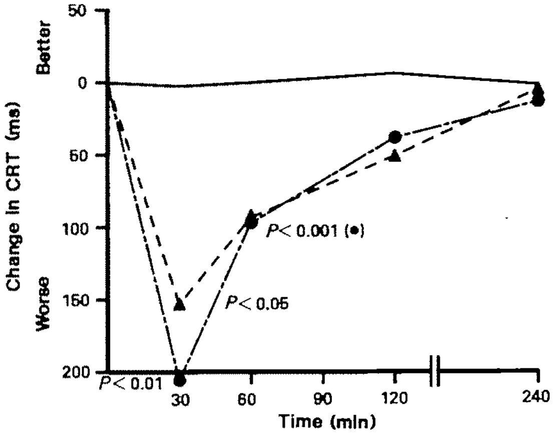

FIG. 5. Mean changes from pre-test baselines of CRT. —— = Control; ▲ = propofol; ● = methohexitone.

acceptable limits and required no specific treatment other than an occasional increase in the rate of i.v. infusion. Interestingly, the mean decrease in systolic arterial pressure of 13 mm Hg 2 min after induction was much less than we found in a previous study of propofol for day-case anaesthesia, in which the mean initial decrease was 30 mm Hg. This difference may be attributable to the fact that patients in the present study had already experienced vasodilatation as a result of the spinal anaesthetic before being subjected to a further vasodilator effect from propofol. The minimal effect of methohexitone on arterial pressure probably reflects a reflex tachycardia (Mackenzie and Grant, 1985).

Similarly, apnoea following induction did not cause a clinical problem, as all patients tolerated an oropharyngeal airway well and it was easy to ventilate their lungs via a face-mask, when this was necessary. Respiratory depression during maintenance was not significant and, indeed, provided a clinical index of anaesthetic depth.

Previous studies with the Cremophor formulation showed that cardiovascular and respiratory depression were dose-related. Briggs and colleagues (1981) found that significant hypotension and apnoea occurred in the majority of patients receiving doses of greater than 2 mg kg^{-1} but were rare in those receiving less. In our study all patients received 2.5 mg kg^{-1} to ensure successful induction of anaesthesia, but it may well be that a smaller dose would be more suitable for routine clinical use and that cardiovascular and respiratory depression would then be less common.

A particular objective of this study was to assess recovery after anaesthesia. Because all patients had undergone spinal anaesthesia, no other drugs were required, and this facilitated direct comparison of propofol with methohexitone. Recovery was rapid in both groups, but quality of recovery was superior following propofol, side effects such as headache, nausea and vomiting occurring much less commonly than after methohexitone. Since anaesthesia was being maintained at an intentionally light level, with the effects of one bolus of induction agent being allowed to wear off before another was given, it is not altogether surprising that there were no differences in recovery times between the groups.

Regional anaesthesia is forming an ever increasing part of everyday anaesthetic practice as anaesthetists become more aware of its potential advantages, for example in relation to certain medical conditions (Aitkenhead and Grant, 1983). However, many patients prefer to be asleep during the actual surgical procedure and several agents have been used to provide hypnosis as an adjunct to the regional block, ranging from sedative drugs to i.v. and volatile anaesthetic agents. To retain the advantages of the regional technique, it is important that recovery from sleep is rapid and relatively free from side effects. An i.v. agent used in this setting must be rapidly eliminated. Propofol, with its early metabolism to pharmacologically inactive metabolites and extremely short distribution and elimination half-lives (2.5 and 50 min respectively (Adam, Kay and Douglas, 1982)) would appear to be a logical agent to use in this manner.

Initial studies with the Cremophor formulation of di-isopropyl phenol tended to support its usefulness for maintenance of anaesthesia, given either by intermittent bolus injection (Rutter et al., 1980; Briggs et al., 1981; Major et al., 1981) or by continuous infusion (O'Callaghan et al., 1982). However, the high incidence of pain on injection and the implication of Cremophor in hypersensitivity reactions (Glen, Hunter and Thomson, 1982) precluded further investigation in this field. Our study with the new emulsion formulation has shown that repeat bolus injection of propofol is an eminently suitable way of providing hypnosis as an adjunct to spinal anaesthesia. Our mean administration rate of 0.130 mg kg^{-1} min^{-1} compares well with the mean infusion rate of 0.120 mg kg^{-1} min^{-1} of the Cremophor formulation in patients undergoing surgery under regional anaesthesia (O'Callaghan et al., 1982), and provides a guideline for future infusion studies with the drug.

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COMPARISON OF INFUSIONS OF PROPOFOL AND METHOHEXITONE TO PROVIDE LIGHT GENERAL ANAESTHESIA DURING SURGERY WITH REGIONAL BLOCKADE

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SUMMARY

General anaesthesia was induced with, and maintained by, an infusion of either propofol or methohexitone, in patients undergoing surgery with the aid of regional blockade. Both agents provided satisfactory and controllable anaesthesia. Complications were few with a similar incidence for the two drugs. Recovery from anaesthesia was significantly faster following propofol.

Although the benefits of performing surgery under regional anaesthesia are well established, the majority of patients prefer to have no memory of the event. This means that some form of sedation is necessary, and the methods used to achieve this include intermittent injections of sedatives or tranquillizers, particularly benzodiazepines (McLure, Brown and Wildsmith, 1983; Dixon et al., 1984), and full general anaesthesia (Scott, 1975). A continuous infusion of an i.v. anaesthetic agent is also a suitable method (Dunnill, 1975; Park and Wilson, 1978; O'Callaghan et al., 1982), but requires that the drug used be rapidly cleared from the body so that accumulation does not occur and recovery is rapid.

Unfortunately, the number of available drugs satisfying the pharmacokinetic criteria for this purpose are few. Althesin has been withdrawn because of an unacceptable incidence of allergic reactions to the solubilizing agent Cremophor, while anaesthetists are reluctant to use etomidate because of its effects on adrenocortical function (Owen and Spence, 1984). Chlormethiazole has never been a popular agent in this country, although it has been described as being close to the ideal sedative to supplement neural blockade techniques (Mather and Cousins, 1980). Di-isopropyl phenol is another i.v. agent which possesses properties suitable for use by infusion, but the original formulation was withdrawn, again because of an unacceptable incidence of allergic reactions.

Recently, di-isopropyl phenol has been re-introduced for evaluation in the form of an emulsion (a 1% w/v aqueous solution in 10% w/v soya bean oil, 1.2% egg phosphatide and 2.25% glycerol) with the generic name propofol. This formulation proved satisfactory for the induction of anaesthesia following a bolus injection, although with some loss of potency compared with the Cremophor preparation (Cummings et al., 1984). It was decided to use a continuous infusion of propofol to supplement regional anaesthesia during surgery, and to compare its effects with those of methohexitone used in a similar manner.

PATIENTS AND METHODS

Sixty adult patients gave their informed consent to take part in the trial, which was approved by the local ethics committee. They were all to undergo general, urological or orthopaedic surgery which would normally be performed under subarachnoid or extradural analgesia, and all were of ASA grades

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1 or 2. Patients with a history of atopy, drug allergy or who were pregnant were not studied. Allocation to receive propofol or methohexitone was on a random basis.

Pre-operative medication was with papaveretum and atropine i.m. approximately 1.5 h before surgery. Thirty-six patients received papaveretum 20 mg, 23 patients received 15 mg and one patient 10 mg; all received atropine 0.6 mg. On arrival of the patient in the anaesthetic room, an i.v. infusion of Hartmann's solution was commenced in a forearm vein and the heart rate and arterial pressure were recorded. The electrocardiogram was continuously displayed. Regional blockade was performed, and all blocks were assessed to ensure their efficacy before general anaesthesia was induced. The local anaesthetic used was bupivacaine in a concentration of 0.5% for subarachnoid blockade and 0.75% for extradural blockade. Adrenaline was not used.

Anaesthesia was induced following establishment of blockade by the slow i.v. injection of either 1% methohexitone or 1% propofol. During induction the patient was asked to count and the time taken from the beginning of the injection to cessation of counting was recorded as the induction time. Note was taken of any pain on injection, involuntary muscle movement, the incidence and duration of any apnoea, and any evidence of allergic reactions.

Immediately following induction, the patient was attached to a continuous infusion of the pure induction agent using a mains/battery operated pump capable of delivering infusion rates from 1 to 150 ml min^{-1} (The Dylade Co. Ltd, Runcorn, Cheshire) so that the infusion could be continued during transfer to the operating theatre. In the early part of the study, the propofol infusion was commenced at a rate of 500 mg h^{-1} but, since this proved inadequate in three patients, the initial rate was doubled thereafter. Methohexitone was infused at an initial rate of 400–500 mg h^{-1}. Once a satisfactory level of anaesthesia was achieved, the rate of infusion was decreased and adjusted to maintain a light level of anaesthesia with eyelash and pupillary reflexes absent. Bolus doses of the induction agent were given if it was necessary to deepen anaesthesia rapidly. All patients breathed oxygen via a Hudson mask during the procedure and an oral or nasopharyngeal airway was used if necessary. The infusion was stopped shortly before the end of surgery.

Arterial pressure and heart rate were recorded automatically at intervals and note was taken of any involuntary movements or periods of apnoea. Atropine was given at the discretion of the anaesthetist, to treat bradycardia. The circulating volume was maintained with Hartmann's solution or whole blood. Metaraminol was given if it was thought necessary to increase rapidly or to prevent any further decrease in arterial pressure.

The times from the cessation of the infusion to the patients opening their eyes on command and giving their correct dates of birth were recorded. Any confusion, restlessness or dreaming during recovery was noted, as was the incidence of nausea and vomiting in the first 24 h after operation. The patients were asked whether they would be prepared to have the same anaesthetic technique again, and the anaesthetist gave an overall assessment of the infusion technique as being good, adequate or poor.

Paired and unpaired Student's *t* tests were used to analyse the results where appropriate. Recovery times were compared following log transformation of the results, as they did not follow a normal distribution.

RESULTS

There were 30 patients in each group, who were comparable with regard to age, weight and sex distribution (table I). The age range was 16–69 yr in each group and all operations were elective procedures. More patients in each group received subarachnoid blockade, but there was no significant difference between the groups.

Table II shows the mean induction dose of propofol to have been 2.14 mg kg^{-1} and that of methohexitone 1.46 mg kg^{-1}. The induction time was slightly longer following propofol, but the difference was not statistically significant. There was no difference between the durations of the infusion in the two groups.

Complications occurring during induction are

TABLE I. *Details of patients and number receiving subarachnoid or extradural analgesia*

	Propofol	Methohexitone
Age (yr) (mean ± SEM)	41.8 ± 2.85	40.2 ± 2.76
Weight (kg) (mean ± SEM)	73.3 ± 2.10	69.5 ± 2.29
Male	19	16
Female	11	14
Extradural	9	13
Subarachnoid	21	17

TABLE II. *Induction and maintenance doses of propofol and methohexitone, with induction times and duration of the infusion in each group (mean ± SEM)*

	Propofol	Methohexitone	P
Induction dose			
(mg)	156.0 ±5.94	101.3 ±3.82	
(mg kg^{-1})	2.14 ±0.068	1.46 ±0.033	
Maintenance dose			
(µg kg^{-1} min^{-1})	102.8 ±5.22	104.2 ±6.31	
Induction time (s)	46.4 ±2.65	41.8 ±3.05	ns
Duration of infusion (min)	44.0 ±2.40	47.3 ±4.01	ns

TABLE III. *Induction complications and incidence and duration of apnoea in the two groups*

	Propofol	Methohexitone
Pain on injection	5 (17%)	5 (17%)
Involuntary movement	5 (17%)	2 (7%)
Hiccup	0	2 (7%)
Apnoea	13 (43%)	9 (30%)
Duration (s)		
(mean ± SEM)	56.0 ± 10.84	34.0 ± 8.16
range	25–145	10–90

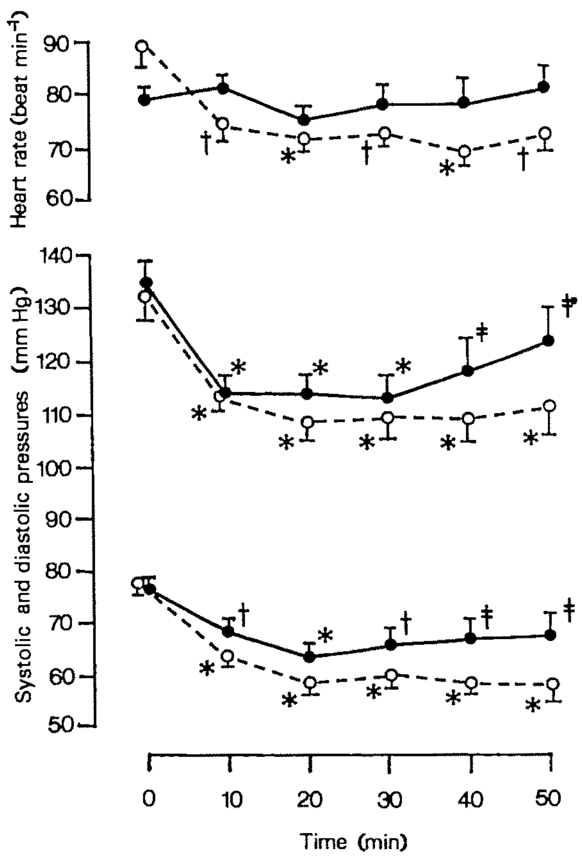

FIG. 1. Changes in heart rate and arterial systolic and diastolic pressures following initiation of regional blockade, and induction and maintenance of anaesthesia with methohexitone (●) and propofol (○). *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

shown in table III. Five patients in each group complained of pain along the vein during injection of the induction agent, which was always given to the rapidly running i.v. infusion; this pain was severe in two of the patients who received propofol. Involuntary muscle movements during induction were few and mild with both drugs. There were no respiratory upsets following propofol, but two patients receiving methohexitone developed hiccup during induction. The incidence and duration of apnoea were both higher in those in whom anaesthesia was induced with propofol, but the difference did not reach statistical significance.

The maintenance doses of both agents were similar: 102.8 µg kg^{-1} min^{-1} for propofol and 104.2 µg kg^{-1} min^{-1} for methohexitone (table II). Initially, there was a tendency to use too low an infusion rate for propofol, but anaesthesia could rapidly be deepened by increasing the rate to maximum for a few minutes. Two patients who received propofol and three given methohexitone required bolus doses. With both drugs, however, control of depth of anaesthesia presented little problem. Involuntary movements during maintenance were mild and insignificant, occurring in five patients who received propofol and three who received methohexitone.

The changes in heart rate and arterial pressure are shown in figure 1. In the control period, the heart rate was significantly faster in the propofol patients. Following induction, and at all times during the maintenance of anaesthesia, the heart rates in those given propofol were significantly lower than during the control period. There was no significant change with methohexitone throughout the procedure. At all times following induction the heart rate in the propofol patients was slower than in those receiving methohexitone, but not significantly so. There were no statistically significant differences in arterial pressure during the control period between the two groups, nor at any time during the infusion, although pressures were always lower in those given propofol. There

TABLE IV. *Recovery times (mean ± SEM)*

	Propofol	Methohexitone	*P*
Opening eyes (min)	4.12 ± 0.37	9.60 ± 1.33	< 0.001
Giving correct date of birth (min)	6.34 ± 0.61	15.4 ± 1.82	< 0.001

was a significant decrease in arterial pressure in both groups following induction, which was maintained throughout the maintenance of anaesthesia. Atropine was required in five patients receiving propofol and in two receiving methohexitone, while metaraminol was given to one of the latter. No patient became apnoeic during the period of infusion.

The recovery times are shown in table IV. Recovery was more than twice as fast in those who received propofol, the difference being significant ($P < 0.001$). Particularly impressive was the clear-headedness of the recovery compared with that following methohexitone, and although only a subjective impression, all the anaesthetists involved in the trial and the recovery room personnel noted this point.

Recovery complications were few in both groups, but tended to be more frequent following methohexitone. Nausea and vomiting occurred in five (17%) of the patients following propofol, compared with eight (27%) after methohexitone. Two patients who received the latter drug were confused and restless during recovery, while two were also crying. Restlessness and confusion were not seen following propofol. No patient would refuse to have either propofol or methohexitone again, although eight of the former and three of the latter would refuse to have another regional block whilst conscious.

Anaesthesia was assessed by the anaesthetist as being good or adequate in all but one patient in each group. There was no evidence of an allergic reaction in any patient.

DISCUSSION

In order for an i.v. anaesthetic agent to be of use by continuous infusion, it must be rapidly cleared from the body so that cumulation is minimal, thus allowing easy control of depth of anaesthesia and rapid, uncomplicated recovery. Clinical studies of the original Cremophor preparation of di-isopropyl phenol indicated that it was suitable for use in this way (Major et al., 1982; O'Callaghan et al., 1982; Fragen et al., 1983) and this was confirmed by the early pharmacokinetic studies (Adam, Kay and Douglas, 1982; Adam et al., 1983).

To date, pharmacokinetic data are not available for the emulsion formulation, propofol, although early studies have shown the ED_{95} to be increased compared with the Cremophor preparation (Cummings et al., 1984). The present study has shown that both the induction dose and that required to maintain anaesthesia by infusion were greater than that found when the original drug was used in a similar manner (O'Callaghan et al., 1982). The depth of anaesthesia was readily and rapidly controllable by altering the rate of infusion, and particularly impressive was the rapid, clear-headed recovery, although detailed investigations of recovery were not made in this preliminary study. This suggests that the pharmacokinetic properties of propofol will confirm its suitability for prolonged infusion.

Because of the varying extent of the sympathetic blockade produced by the regional technique, it was not possible to make any definite comment on the cardiovascular effects of the two drugs. However, the use of propofol was associated with a significant decrease in heart rate and at all times this was lower, although not significantly so, than in patients receiving methohexitone. In both groups there was a significant decrease in arterial pressure from the control period and again this was lower (not statistically significant) in those who received propofol. The cardiovascular changes produced by the latter were very similar to those found with the original preparation when used in the manner described here (O'Callaghan et al., 1982).

Methohexitone has been used quite extensively as a sole anaesthetic agent by intermittent injection and by infusion for such procedures as tonsillectomy in children (Liscombe, 1968), conservative dentistry (Mann et al., 1971) and bronchoscopy (Hargrove and Pearce, 1964; McIntosh et al., 1979) and also to supplement nitrous oxide anaesthesia (Hunter, 1972; Prys-Roberts et al., 1983). Earlier investigations on blood concentrations were unable to explain the more rapid recovery following methohexitone than following thiopentone (Sunshine et al., 1966), but the development of more sensitive assay techniques showed that the elimination half-life of methohexitone was relatively short (Breimer, 1976). The decrease in liver blood flow during anaesthesia and surgery will result in an increase in half-life compared with that found in volunteers (Hudson, Stanski and Burch, 1982). However, the pharmacokinetics of methohexitone are such that cumulation does occur after doses in excess of 600–800 mg (Sear, 1983) and hence it is not a suitable drug for infusions in excess of about 2 h.

In the present study both agents produced satisfactory anaesthesia to supplement regional blockade. The mean maintenance dose of methohexitone 104 $\mu g\ kg^{-1}\ min^{-1}$ was higher than that reported to supplement nitrous oxide anaesthesia (Hunter, 1972; Prys-Roberts et al., 1983); there are no comparable figures yet available for propofol. The incidence of complications associated with the two drugs was similar, although severe pain on injection occurred only with propofol. This remains a problem. The important difference between the techniques was the rapidity and quality of recovery following propofol.

With the withdrawal of Althesin and the current ban on infusions of etomidate in the intensive care unit, there is an urgent need for an i.v. anaesthetic that can be given over prolonged periods without accumulation and allowing rapid recovery. The findings reported here strongly suggest that propofol would meet these requirements, but more extensive clinical trials are necessary to establish its role in this respect.

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INCREMENTAL PROPOFOL FOR SHORT PROCEDURES

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SUMMARY

Propofol was used to induce and maintain anaesthesia in patients undergoing minor gynaecological procedures. Quality of anaesthesia, the rate of recovery and the influence of different methods of premedication were assessed. Unpremedicated patients required a higher induction dose than those premedicated with either lorazepam or papaveretum and hyoscine, but maintenance dose requirements were comparable. Regardless of premedication, there were similar decreases in mean arterial pressure, although respiratory function recovered more rapidly in patients premedicated with lorazepam. No significant changes in heart rate were noted in any group. The overall incidence of pain on injection was 3.7% (lignocaine 0.5 mg added to each 9.5 mg of propofol) and a skin rash occurred in 6% of patients. All patients recovered rapidly and uneventfully.

The new i.v. induction agent 2, 6 di-isopropyl phenol is poorly water soluble and therefore cannot be formulated as a simple aqueous solution. When it was first introduced, Cremophor EL was used as the solvent; recently, 2, 6 di-isopropyl phenol has been reformulated as an emulsion in soya bean oil.

The preparation containing Cremophor EL was studied widely, and several investigators demonstrated that 2, 6 di-isopropyl was a rapidly-acting agent (Briggs et al., 1981) which produced good quality anaesthesia with few excitatory side effects (Rogers et al., 1980; Kay and Stephenson, 1981; Briggs et al., 1982); recovery was reported to be rapid and pleasant (Jones, 1982). However, there have been occasional reports of anaphylactoid reactions (Briggs, Clarke and Watkins, 1982), which may have been caused by the Cremophor EL. Moreover, pain on injection to a vein on the dorsum of the hand occurred in 40–70% of patients. A preparation containing a lower concentration of di-isopropyl phenol was evaluated (Kay and Rolly, 1977; Rogers et al., 1980; Briggs et al., 1981), but the incidence of pain on injection remained unaltered.

It is possible that the reformulation of di-isopropyl phenol as an emulsion may have altered its characteristics as an anaesthetic agent. For instance, Cummings and his colleagues (1984) demonstrated that the required induction dose was slightly greater with the soya bean oil preparation.

In a short pilot study (Brooker, Stafford and Hull, 1985), we found that 40% of patients receiving the new preparation complained of pain following injection to a vein on the dorsum of the hand. However, the incidence of pain was greatly reduced by the addition of lignocaine to the emulsion within 5 min of use.

The present study was designed to evaluate the new preparation of di-isopropyl phenol (propofol) in an incremental technique for minor gynaecological procedures. The quality of anaesthesia, the rate of recovery and the influence of different methods of premedication were assessed.

PATIENTS AND METHODS

One hundred and thirty four women (ASA I-II) aged between 16 and 70 yr, due to undergo cervical dilatation and curettage or termination of pregnancy, gave written permission for inclusion in the study. The use of propofol had been approved by the Committee for Safety of Medicines and the Hospital Ethics Committee.

Patients in the study were numbered consecutively. Each number was pre-assigned to one of three premedication regimens by a computer-generated random scheme, using a permuted block

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TABLE I. *Details of patients studied*

	Group 1	Group 2	Group 3
Number of patients	44	45	45
Age (yr) (mean and range)	34.0 (19–53)	33.3 (16–60)	36.0 (16–70)
Weight (kg) (mean and SD)	59.5 (9.15)	58.4 (9.69)	59.4 (9.78)

TABLE II. *Doses of propofol (mean (SD)), recovery times (25–75 percentiles), and the incidence of nausea or vomiting (percentage of patients in each group)*

	Group 1	Group 2	Group 3
Induction dose (mg)	103 (23)	100 (18)	126 (27)
Maintenance dose (mg min^{-1})	11.5 (6.32)	12.3 (6.67)	12.3 (5.2)
Recovery time (min)	4.8 (3.7–6.5)	4.9 (3.5–5.5)	4.5 (3.6–5.3)
Incidence of nausea or vomiting (%)	2.6	17.5	2.6

of size 3, and the patients were premedicated accordingly:

Group 1 = lorazepam 1 mg by mouth 2 h before operation;
Group 2 = papaveretum 10 mg i.m. with hyoscine 0.2 mg i.m. 1 h before operation;
Group 3 = not premedicated.

In order to minimize pain on injection, lignocaine 0.5 mg was added to each 9.5 mg of propofol throughout.

Mean arterial pressure (MAP) and heart-rate were measured at 1-min intervals using an oscillometric monitor (Dinamap). Expiratory flow was measured by means of a Magtrak respirometer (Ferraris Engineering Co.), and each expiratory volume calculated by integration. All data were collected using a mobile computer-based system (Stafford, Brooker and Hull, 1984). This system recorded details of drug administration and the times at which events occurred during the anaesthetic procedure. Each expiration was timed (to an accuracy of 1 ms) from the start of induction and recorded with the calculated volume.

Immediately before induction, arterial pressure and respiratory data were collected for a 1-min "control" period while patients breathed 100% oxygen via a face mask.

Following the control period, each patient received a bolus of alfentanil 250 µg i.v. Propofol (with lignocaine) was injected to a vein on the dorsum of the hand at a rate of 9.5 mg every 10 s until the eyelash reflex could no longer be elicited. At this point a further 1 ml of propofol was given. All patients undergoing termination of pregnancy then received syntocinon 10 units i.v. Throughout induction, all patients breathed 100% oxygen.

Anaesthesia was maintained by incremental doses of propofol. After induction, patients breathed 60% nitrous oxide in oxygen until the end of cervical dilatation, thereafter breathing 100% oxygen.

Recovery time was assessed as the interval between the last incremental dose of propofol and the mean of the times at which the patient protruded her tongue and showed her left thumb on command.

Measurements derived from the three groups were compared, using one-way analysis of variance followed by Tukey's procedure for the comparison of multiple means for normally distributed data, and Kruskal–Wallis analysis of variance of ranks followed by Wilcoxon's rank sum test for results that were not normally distributed. Differences within each group were compared using paired Student's *t* tests or the Sign test where appropriate. Frequencies of observations were compared using contingency tables and Chi squared analysis. 2 × 2 Contingency tables were analysed using Fisher's exact test. A probability of less than 0.05 was taken to represent statistical significance.

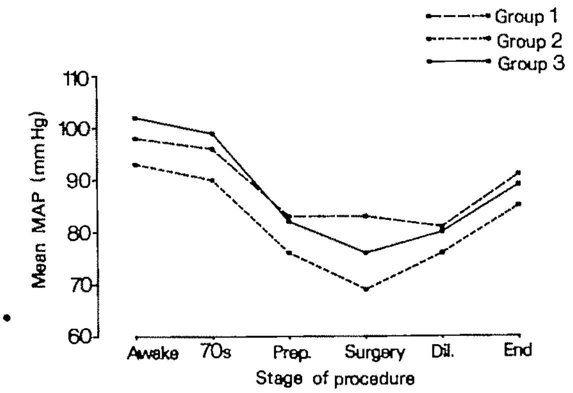

FIG. 1. Mean arterial pressure during main stages of procedure. Awake = 60 s before start of anaesthesia; 70 s = first 70 s of anaesthesia; Prep. = at start of skin preparation; Surgery = at start of surgery; Dil. = at end of cervical dilatation; End = at end of procedure.

RESULTS

Patients in the three groups were comparable with respect to age and weight (table I).

The mean dose of propofol required to induce anaesthesia in group 3 (unpremedicated) patients was significantly greater ($P < 0.01$) than those given to patients in groups 1 or 2 (table II).

We could not establish any correlation between the induction dose and either age or weight, in any group. The mean dose rate of propofol required for the maintenance of anaesthesia was similar in all groups. Combining data from the three groups, the mean (SD) maintenance dose was 12.0 (±6.1) mg min^{-1}.

The overall incidence of pain on injection was 3.7% and there were no significant differences between the three groups. No patient developed involuntary muscle movement, hiccup or other excitatory effects. Eight patients developed transient erythema after induction. In three this was confined to a local flare, four patients developed erythema only in the "blush" area, and one patient developed widespread erythema. No patient developed bronchospasm or severe hypotension.

Evoked movement was recorded continuously as slight, moderate, or too vigorous to permit surgery. Overall, 43% of patients made moderate responsive movements at some time during the course of the procedure, but only 10 moved for more than 30 s. There were no statistically significant differences in the frequency or severity of evoked movements between the three groups.

Figure 1 and table III show the mean values for MAP in each group of patients at different stages of the procedure. During the control period there was a statistically significant difference ($P < 0.01$) between the mean arterial pressures recorded from patients in group 3 (unpremedicated) and those in group 2 (papaveretum and hyoscine). Following induction, the mean arterial pressure decreased significantly in all groups. The degree of hypotension correlated with the total dose of propofol given ($r = 0.2467$, $P_{(\rho=0)} < 0.02$). However, there were no significant differences between the groups. At the "skin preparation" stage, the average MAP was significantly lower ($P < 0.05$) than during the preoperative control period, and remained so until the end of the procedure. No consistent changes in heart rate were noted (fig. 2, table IV).

The ventilatory minute volumes measured during the control period differed between the groups, those receiving papaveretum and hyoscine (group 2) having a lower value than the unpremedicated (group 3) patients (fig. 3, table V). At "skin preparation", all groups showed a marked reduction in minute volume, but there were no statistically significant differences between the groups. By the "start of surgery", patients in group 1 (lorazepam) had a significantly higher minute volume than those in groups 2 and 3, and this difference persisted until after cervical dilatation.

Post-induction apnoea lasting for 40 s or more occurred in 32% of patients and, in 3.6% of

TABLE III. *Mean arterial pressure (mm Hg) (mean ± SEM) at different stages of the procedure. Awake = 60 s before the start of anaesthesia; 70 s = first 70 s of anaesthesia; Prep. = until start of skin preparation; Surgery = to start of surgery; Dil. = to end of cervical dilatation; End = to end of procedure*

	Awake	70 s	Prep.	Surgery	Dil.	End
Group 1	98±2.3	96±2.3	83±2.7	77±2.7	81±2.4	91±2.2
Group 2	93±1.9	90±2.2	76±1.7	69±1.9	76±2.8	85±2.1
Group 3	102±2.4	99±2.4	82±1.9	76±2.9	80±2.9	89±2.2

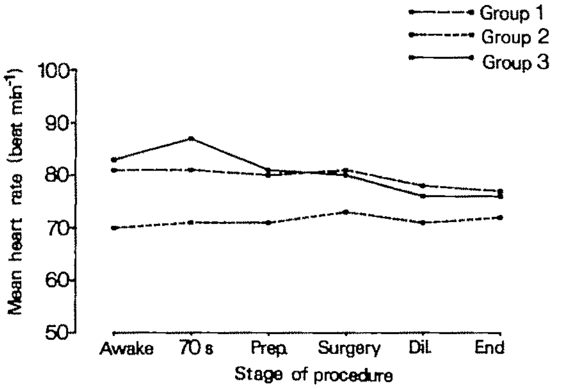

FIG. 2. Heart rate during main stages (as in figure 1) of procedure.

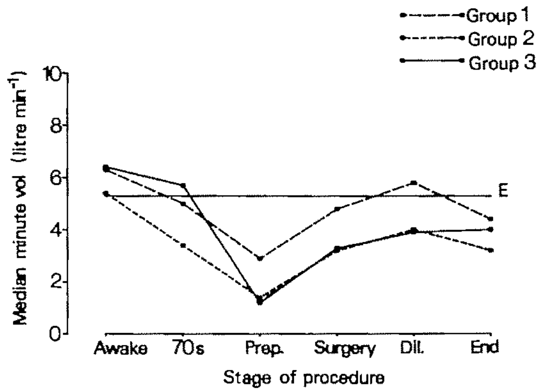

FIG. 3. Minute volume at main stages (as in figure 1) of procedure. Line E represents the expected value for a 60-kg female volunteer (Dittmer and Grebe, 1958).

patients, this apnoeic period lasted for more than 100 s. There were no significant differences between the incidence, or duration, of apnoea in the three goups.

All patients recovered uneventfully. The median recovery times (from last propofol increment) did not differ significantly (table II). Combining the results from all groups yielded an overall median recovery time of 4.7 min, with a 25–75 inter-centile range of 3.6–6.1 min. Postoperative nausea or vomiting was rare except in the patients who had received papaveretum (group 2), in whom the incidence was 17.5%.

DISCUSSION

In this investigation, the induction dose of propofol did not correlate with either the age or the weight of a patient. This finding may appear to conflict with that of Robinson, Dundee and Halliday (1985) who demonstrated a significant decrease in induction dose in patients more than 60 yr of age. However, since the present study included only two patients in this age range, the lack of correlation is not surprising.

Pain on injection to veins on the dorsum of the hand remained a problem with the new formula-

TABLE IV. *Heart rate (beat min^{-1}) (mean ± SEM) at different stages of the procedure*

	Awake	70 s	Prep.	Surgery	Dil.	End
Group 1	81 ± 2.1	81 ± 2.4	80 ± 1.7	81 ± 3.1	78 ± 2.0	77 ± 2.2
Group 2	70 ± 2.3	71 ± 2.3	71 ± 1.9	73 ± 2.2	71 ± 2.1	72 ± 2.1
Group 3	83 ± 2.1	87 ± 2.5	81 ± 1.9	80 ± 2.0	76 ± 1.9	76 ± 1.9

TABLE V. *Minute volume (litre min^{-1}) (median, 25th and 75th percentiles) at different stages of the procedure*

	Awake		70 s		Prep.		Surgery		Dil		End	
Group 1	6.3	4.2 7.8	5.0	2.3 6.6	2.9	0.7 5.2	4.8	3.5 7.3	5.8	4.7 7.1	4.4	3.1 5.8
Group 2	5.4	3.9 6.7	3.4	1.2 5.1	1.4	0.5 3.7	3.2	1.3 4.4	4.0	1.7 5.9	3.2	2.2 4.3
Group 3	6.4	5.4 8.9	5.7	3.6 6.7	1.2	0.4 3.6	3.3	0.8 5.1	3.9	2.6 5.6	4.0	2.9 4.9

tion, and a pilot study suggested that the addition of lignocaine may reduce the incidence to an acceptable level (Brooker, Stafford and Hull, 1985). The present results confirm those findings, since the overall incidence of pain on injection was 3.7%. We consider this to be clinically acceptable.

Significant ventilatory depression developed in all three groups, and this may have been (at least partly) the result of the small pre-induction dose of alfentanil. The horizontal line in figure 3 represents the expected minute volume of a trained 60-kg subject (Dittmer and Grebe, 1958). Comparing this with our results, it is seen that, during the control period, the unpremedicated patients and those in group 1 had higher minute volumes than predicted. By the start of surgery, the lorazepam premedication group (1) had a significantly higher minute volume than those in groups 2 and 3, and this remained so until the end of surgery. The patients who had received premedicant drugs required similar incremental dose rates of propofol, and it is likely that the differences in minute volume between the lorazepam and papaveretum groups were attributable to the respiratory depressant effects of opioid premedication. During surgery, the unpremedicated patients demonstrated more respiratory depression than those premedicated with lorazepam, possibly as a result of the higher dose of propofol which they required.

We found a slightly higher incidence of apnoea than Kay and Stephenson (1981), who found that four of 20 patients were apnoeic for more than 30 s. However, our 32% incidence of apnoea (lasting for 40 s or more), was less than that of Rolly, Versichelen and Zubair (1980), who found that 55% of patients were apnoeic for a mean time of 64 s. It would appear, therefore, that the change in formulation has not greatly modified the respiratory depressant properties of di-isopropyl phenol. Since there were no significant differences between groups in respect of the incidence or duration of apnoea, it is concluded that the choice of premedication is not a major factor.

The observed (24 mm Hg) mean decrease in MAP was very similar to that noted by Prys-Roberts and colleagues (1983). Using the original preparation, they found a decrease in MAP of 27 mm Hg before the start of surgery. As in the present study, they observed no significant changes in heart rate. Thus it appears that the haemodynamic effects of the two preparations are similar.

It is concluded that the anaesthetic technique described here provides good quality anaesthesia with no excitatory phenomena, minimal nausea or vomiting and a low incidence of pain on injection. However, significant respiratory depression and decreases in arterial pressure do occur. As expected, choice of premedication has some influence on the degree of respiratory depression. It is of particular concern that skin reactions occurred in 6% of patients, and it is important that the significance of these be established.

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CARDIOVASCULAR RESPONSES TO TRACHEAL INTUBATION IN SMALL CHILDREN

Effects of the Induction of Anaesthesia with Halothane

L. LINDGREN AND L. SAARNIVAARA

SUMMARY

Cardiovascular changes in 27 children (mean age 1.5 yr) were studied during the induction of anaesthesia with 2.5% halothane and 70% nitrous oxide in oxygen. The eyelash reflex disappeared in a mean of 62±3.6 (SEM) s and tracheal intubation could be performed 4.9±0.2 min after the start of halothane anaesthesia. Intubating conditions were satisfactory in 85% of the children. Systolic arterial pressure increased by 10.8±1.9 mm Hg and diastolic pressures by 6.0±1.4 (SEM) mm Hg after intubation of the trachea. Heart rate decreased significantly after induction. No cardiac arrhythmias were noted. There were no significant changes in Q–T interval after induction, after intubation or during the later course of the anaesthetic.

The i.v. induction of anaesthesia is followed by circulatory responses to tracheal intubation such as increases in arterial pressure, heart rate and the rate–pressure product (Kautto, 1981), prolongation of the Q–T interval on the electrocardiogram and cardiac arrhythmias, in both children and adults (Saarnivaara and Lindgren, 1983). Therefore, from a cardiovascular point of view, the i.v. induction of anaesthesia may be less than ideal. A previous study noted that the circulatory responses to tracheal intubation after an inhalation induction (enflurane followed by suxamethonium) were considerably attenuated when compared with those associated with an i.v. induction with thiopentone and suxamethonium (Lindgren and Saarnivaara, 1983).

Although halothane is used commonly for the induction of anaesthesia in small children, and provides ideal intubating conditions without the use of suxamethonium (Yakaitis, Blitt and Angiulo, 1977), there are no studies on the cardiovascular responses to tracheal intubation when halothane has been used to induce anaesthesia in children.

The present work was designed to study inhalation induction of anaesthesia with halothane in small children, with special reference to cardiovascular responses to tracheal intubation.

PATIENTS AND METHODS

Twenty-seven children were studied (table I). They were premedicated with triclofos 70 mg kg^{-1} and atropine 0.03 mg kg^{-1} by mouth, approximately 90 min before the induction of anaesthesia. Halothane 2.5% was administered with 70% nitrous oxide in oxygen, a Rees modification of the Ayre's T-piece with a face mask being used. Twice the average value for minute ventilation was used as listed in Documenta Geigy Scientific Tables (Ciba–Geigy Ltd, 1975) as fresh gas flow. The times from the start of anaesthesia to the disappearance of eyelash reflex and to tracheal intubation were recorded with a stop-watch. The clinical signs of adequate depth of anaesthesia for

TABLE I. *Characteristics of the children. Mean ±SD for 27 subjects*

Male/Female	Age (yr)	Weight (kg)	Haemoglobin concn (g $litre^{-1}$)
17/10	1.5±0.6	11.2±1.9	125±7.6

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TABLE II. *Intubating conditions after halothane induction. Percentage numbers for 27 children. Good = vocal cords open and motionless; acceptable = small movements in vocal cords; unsatisfactory = coughing after intubation*

Good	Acceptable	Unsatisfactory
74	11	15

tracheal intubation were: fixed and small pupils, relaxation of the jaw and regular, free diaphragmatic breathing. Intubating conditions were classified as *good* if the vocal cords were open and motionless, *acceptable* if slightly moving and *unsatisfactory* if the child was coughing after intubation (table II). Systolic and diastolic arterial pressures were measured indirectly (Riva–Rocci method) before induction, and immediately before and after tracheal intubation as well as 5 min after intubation. Heart rate and the ECG (lead AVR) with three surface electrodes were displayed continuously on an oscilloscope and recorded at a paper speed of 25 mm s^{-1}. Monitoring was started 1 min before induction. The Q–T interval was measured before induction, immediately before and after, and 5 min after, tracheal intubation. The Q–T interval was measured from the onset of the QRS-complex to the end of the T-wave. On each occasion the mean Q–T interval from four successive beats was determined. Heart rate correction was made according to the formula: $Q{-}T_c = Q{-}T/\sqrt{RR}$. Values less than 440 ms were considered to be normal (Bazett, 1920). At the beginning of the operation, the otolaryngologist classified the antisialagogue effect as *satisfactory* if the oropharynx was dry or moist and as *unsatisfactory* if it was wet or very wet (Boyd and Manford, 1973). All the children were anaesthetized by the same author (L.S.)

Student's *t* test was used for the statistical analysis of the results. All data are given as mean ± SEM.

RESULTS

The eyelash reflex disappeared in 62 ± 3.6 s and tracheal intubation was possible 4.9 ± 0.2 min after the start of anaesthesia. Intubating conditions were good in 74%, acceptable in 11% and unsatisfactory in 15% of the children (table II). Immediately before intubation, the mean decreases in systolic and diastolic arterial pressures from the control values were 22 and 11 mm Hg, respectively. After tracheal intubation, the mean increases in systolic and diastolic arterial pressures from the values measured immediately before intubation were 11 and 6 mm Hg, respectively. The values measured 5 min after intubation did not differ

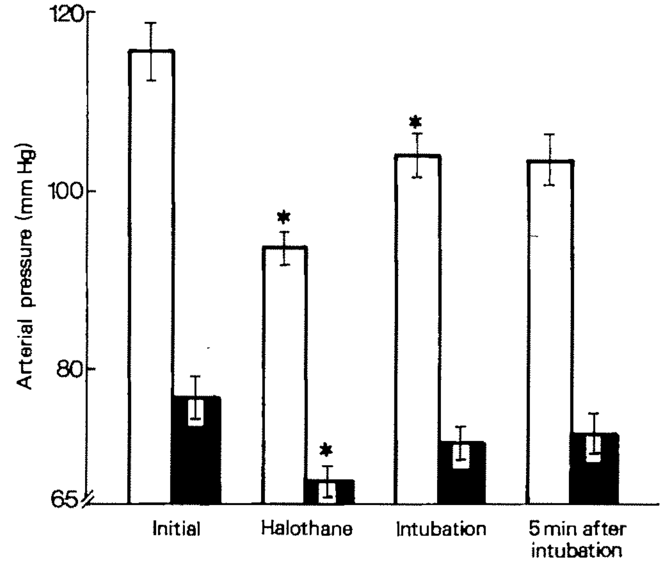

FIG. 1. Systolic (□) and diastolic (■) arterial pressure during induction of anaesthesia with 2.5% halothane plus 70% nitrous oxide in oxygen. Mean values for 27 children. Bars indicate SEM. $^*P < 0.001$: significant difference from the corresponding preceding arterial pressure.

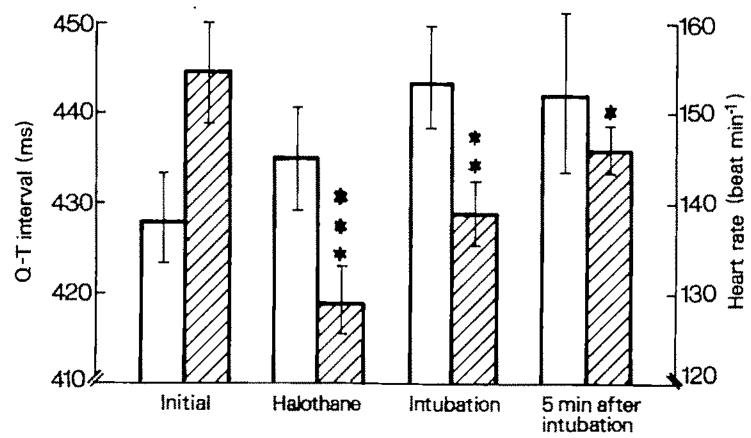

FIG. 2. Q–T intervals (ms) (☐) and heart rate (beat min^{-1}) (▨) during induction of anaesthesia. Mean values for 27 children: initial value; 4.9±0.9 (SD) min after inhalation of 2.5% halothane with 70% nitrous oxide in oxygen (Halothane); after intubation (Intubation); 5 min after intubation. Significant differences from the preceding heart rate: $***P < 0.001$; $**P < 0.01$; $*P < 0.02$.

significantly from the values obtained immediately after intubation (fig. 1). Values for arterial pressure from all the children were included in the results.

The antisialagogue effect was satisfactory in 87% and unsatisfactory in 13% of the children at the beginning of the operation. The mean preanaesthetic Q–T interval was 428±5.3 ms. There were no significant changes in Q–T interval during the induction of anaesthesia. The mean control heart rate was 155 beat min^{-1} before the start of anaesthesia and decreased significantly ($P < 0.001$) by a mean value of 26 beat min^{-1} during the 4.9±0.2 min of anaesthesia before tracheal intubation (fig. 2). Cardiac arrhythmias were not seen.

DISCUSSION

Inhalation induction of anaesthesia with halothane and 70% nitrous oxide in oxygen resulted in minimal cardiovascular responses to tracheal intubation. No cardiac arrhythmias were recorded at any time.

Intubating conditions

Tracheal intubation could be performed satisfactorily in 85% of the children. The MAC of halothane for endotracheal intubation in children aged 4 yr is 1.33% in oxygen (Yakaitis, Blitt and Angiulo, 1977). Since in the present study, halothane, was administered in 70% nitrous oxide in oxygen, the MAC for tracheal intubation was 0.42% (Saidman and Eger, 1964). Although the end-tidal concentration of halothane was not measured in the present study, end-tidal concentrations of 0.8% have been reported with inspired concentrations of 2% after 3 min administration of halothane to children (Lindgren, 1981a). In the present study, inspired 2.5% halothane with 70% nitrous oxide in oxygen was adequate for tracheal intubation within about 5 min.

Cardiovascular responses

The increase in systolic arterial pressure after intubation was within the same range as that seen with enflurane (Lindgren and Saarnivaara, 1983) and was less marked in the present study than noted previously by Saarnivaara (1977) and Lindgren, Saarnivaara and Himberg (1980) with thiopentone followed by suxamethonium. Laryngeal responses are not inhibited by barbiturates (Goodman and Gilman, 1980) and therefore halothane, like enflurane (Lindgren and Saarnivaara, 1983), seems to be preferable to thiopentone for laryngeal and tracheal manipulation.

The Q–T interval was not prolonged significantly during the induction of anaesthesia or the intubation of the trachea during halothane anaesthesia. Usually, the Q–T interval is shorter during the administration of halothane in children (Lindgren, 1981b). However, should the Q–T interval before anaesthesia be prolonged, serious ventricular arrhythmias may be associated with the use of halothane during oral (Lindgren, 1981b) or general surgery (Wig et al., 1979). Since such prolongation of the Q–T interval can be reversed when the ventricular arrhythmia is treated with lignocaine (Lindgren, 1981b), we believe that prolongation of the Q–T interval, in association with the use of halothane, is a predictor of ventricular arrhythmia.

There is evidence that the Q–T interval is prolonged in the presence of high serum concentrations of catecholamines. Prolongation of the Q–T interval during a hypertensive period has been found in patients with phaeochromocytoma (Cheng and Bashour, 1976); increased serum noradrenaline concentrations have been demonstrated during manipulation of this tumour (Takki et al., 1972). Prolongation of the Q–T interval has been found after the injection of noradrenaline to dogs (Abildskov, 1976). Tracheal intubation also causes a sympathoadrenal stimulus (Tomori and Widdicombe, 1969), and increased arterial noradrenaline concentrations and increases in arterial pressure have been observed after intubation in adults (Russel et al., 1981). Therefore, tracheal intubation may cause prolongation of the Q–T interval associated with high serum catecholamine concentrations. Cardiac arrhythmias occur frequently after tracheal intubation in children (Saarnivaara and Lindgren, 1983). Halothane sensitizes the heart to the arrhythmogenic effect of catecholamines (Katz and Katz, 1966). Therefore, arrhythmias might be expected to develop after tracheal intubation during halothane anaesthesia.

In the present study, however, both the increase in arterial pressure and changes in Q–T interval after tracheal intubation were minimal and no cardiac arrhythmias were noted. This result may reflect the fact that halothane itself inhibits the burst of efferent sympathetic activity (Deutsch et al., 1962) caused by tracheal intubation. Therefore, halothane here may prevent the prolongation of the Q–T interval, the increase in arterial pressure and cardiac arrhythmia. On the other hand, after manipulations like dissection of the tonsils, sympathetic activity may increase by a different mechanism, resulting in prolongation of the Q–T interval and cardiac arrhythmia in the presence of halothane (Lindgren, 1981b). Consequently, tracheal intubation may not be comparable to tonsillectomy in regard to stimulation of sympathetic activity.

The present results confirm the earlier findings that halothane markedly inhibits laryngeal reflexes and facilitates tracheal intubation (Price, 1975; Yakaitis, Blitt and Angiulo, 1977). The heart rate decreased significantly during the induction of anaesthesia in our study. This may have been the result of the inhibition of the firing rate of the sinoatrial node caused by halothane (Flacke and Alper, 1962; Hauswirth and Schaer, 1967).

Thus, the induction of anaesthesia with halothane in small children provided adequate anaesthesia for tracheal intubation with minimal cardiovascular response, stabilization of Q–T interval and normal cardiac rhythm.

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VENTILATORY RESPONSES TO REBREATHING AND CARBON DIOXIDE INHALATION DURING ANAESTHESIA IN CHILDREN

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SUMMARY

In 12 spontaneously breathing intubated children (9.3–25 kg), ventilatory responses to rebreathing and to the inhalation of carbon dioxide (CO_2) were investigated during halothane anaesthesia for minor surgical procedures. A T-piece (Mapleson F system) was used, modified by the insertion of a pneumotachograph and a paediatric airway adaptor of an in-line capnograph in the patient limb. Exhaled gas was collected for determination of expired CO_2 content. Measurements were made when the fresh gas flow (FGF) was at the borderline for rebreathing (FGF_r) and during 10 min with a mean FGF 44% lower, producing a maximal inspired CO_2 ($I_{CO_2\,max}$) (%) of 1.45 ± 0.38% (mean ± 1 SD). Measurements were repeated 5 min after returning to a flow exceeding FGF_r and then during CO_2 inhalation for 10 min after the addition of 1.24 ± 0.32% CO_2 (mean ± 1 SD) to this flow. During both rebreathing and CO_2 inhalation end-tidal CO_2 (E'_{CO_2}) was unchanged and $\dot{V}E$ did not increase significantly (18%), but during CO_2 inhalation alveolar ventilation increased ($P < 0.05$), indicating an adequate and intact response to this level of CO_2 inhalation. Estimations of $I_{CO_2\,max}$ could be made from the expression: $I_{CO_2\,max}(\%) = -0.7 \times FGF/\dot{V}E + 2.5$ and FGF to minute ventilation ($\dot{V}E$) ratios lower than 1 were found to produce $I_{CO_2\,max}$ of 1.8% or higher. Such low FGF are likely to result in rebreathing within the alveolar ventilation and are thus of clinical importance. We believe that to increase the margin of safety in anaesthetized spontaneously breathing children, FGF of at least 1.5 to 2 times $\dot{V}E$ should be used.

Rebreathing may occur at low fresh gas flows in anaesthetic breathing systems such as the T-piece and its modifications, and to prevent this, it has been suggested that fresh gas flows of at least 2.5 to 3 times the actual minute ventilation be used (Conway, Seeley and Barnes, 1977; Ungerer, 1978; Byrick, 1980; Nott, Walters and Norman, 1982; Lindahl, Charlton and Hatch, 1984). However, there is debate as to whether a moderate degree of rebreathing need be avoided (Dean and Keenan, 1982; Spoerel, 1983). In 1968, Kain and Nunn reported criteria for rebreathing based upon the view that carbon dioxide rebreathing was not clinically important until it occurred within alveolar ventilation. More recently, Meakin and Coates (1983) concluded, from calculations of the degree of rebreathing using a mathematical model, that fresh gas flows equal to minute ventilation would not result in clinically significant rebreathing in Mapleson D systems, according to the Kain and Nunn criteria. These criteria are given below and one of the three has to be fulfilled:

I. Minute ventilation increased by more than 10% while end-tidal carbon dioxide tension remained unchanged or increased.

II. Minute ventilation was unchanged and end-tidal CO_2 tension increased by more than 0.7 kPa.

III. Minute ventilation increased by more than

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TABLE I. *Patient data. P/H = Papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1} i.m.; P/A = pethidine compound (1 ml contains: pethidine 25 mg, promethazine 6.25 mg, chlorpromazine 6.25 mg) 0.07 ml kg^{-1} and atropine 0.2–0.4 mg i.m.; A = atropine 0.02 mg kg^{-1} i.m.; H = halothane; C = caudal analgesia with 0.25% bupivacaine 0.5 ml kg^{-1}*

Patient No.	(yr	Age months	weeks)	Body weight (kg)	Operation	Premedication	Anaesthesia
1	4	4	0	17.1	Correction of squint	P/H	$O_2/N_2O/H$
2	5	3	0	25.0	Correction of squint	P/H	$O_2/N_2O/H$
3	1	9	0	14.5	Epispadia repair	P/H	$O_2/N_2O/H/C$
4	2	10	0	13.8	Epispadia repair	P/H	$O_2/N_2O/H/C$
5	2	11	0	12.2	Hypospadia repair	P/A	$O_2/N_2O/H/C$
6	1	10	0	10.2	Hypospadia repair	P/A	$O_2/N_2O/H/C$
7	3	1	3	8.5	Resection of urethral valves	P/A	$O_2/N_2O/H$
8	4	9	0	15.5	Investigation Conjunctival biopsy	P/H	$O_2/N_2O/H$
9	4	1	2	15.0	Epispadia repair	P/A	$O_2/N_2O/H/C$
10	1	4	0	9.3	Bilateral cleft lip and palate repair	A	$O_2/N_2O/H$
11	2	11	0	11.2	Excision of bronchial fistula	P/A	$O_2/N_2O/H$
12	3	6	2	13.8	Hypospadia repair	P/A	$O_2/N_2O/H/C$

5%, together with and end-tidal CO_2 tension increased by more than 0.3 kPa.

In the present study the ventilatory responses to rebreathing caused by low fresh gas flows and by the addition of CO_2 to inspired gas were studied during halothane anaesthesia in spontaneously breathing children. Relationships between actual minute ventilation, fresh gas flow and maximal inspired CO_2 concentrations were determined and the clinical importance of rebreathing evaluated.

PATIENTS AND METHODS

The ventilatory responses to rebreathing at low fresh gas flows (FGF) and to the inhalation of CO_2 as reflected by minute ventilation ($\dot{V}_E$), tidal volume (V_T), respiratory rate (f) and end-tidal CO_2 concentration (E'_{CO_2}) were followed during halothane anaesthesia and surgery in 12 intubated, spontaneously breathing children. Body weights ranged from 9.3 to 25 kg and ages from 1 to 5 yr. All patients were free from cardiorespiratory disease. Further patient data are presented in table I.

Anaesthesia was induced with cyclopropane in oxygen ($F_{I_{O_2}}$ 0.5) and tracheal intubation was facilitated by the injection of suxamethonium chloride 1–1.5 mg kg^{-1} i.v. Respiration was spontaneous throughout and anaesthesia maintained with nitrous oxide and 0.5–2.0% halothane in oxygen. For genital procedures, caudal analgesia was established after the induction of anaesthesia with 0.25% bupivacaine 0.5 ml kg^{-1}. The anaesthetic system was a modified T-piece (Mapleson F system) (fig. 1). Arterial pressure and heart rate were measured automatically at regular intervals (Dinamap 850, Applied Medical Research, Tampa, Florida, U.S.A.). A heated pneumotachograph (Fleisch No. 0) and the paediatric airway adaptor of an in-line capnograph (Hewlett–

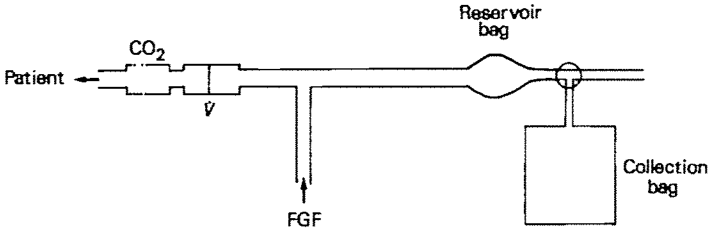

FIG. 1. The anaesthetic system used. CO_2 indicates the position of the in-line capnograph and $\dot{V}$ the position of the pneumotachograph.

Packard, 14360 A) were placed in the patient limb of the T-piece. $\dot{V}\text{E}$ was measured by electrical integration of the flow signal from a differential pressure manometer (Validyne MP45-1-871, range ± 2 cm H_2O). E'_{CO_2} was measured from the recorded CO_2 signal and an easily identified plateau phase was required in all cases. The response time of the capnograph was 0.05 s which, from a technical point of view, allowed registration of end-tidal CO_2 values from a plateau phase at respiratory rates well above those seen in this study. Expired gas passed to a dry gas meter (Standard Gas Meter, AB Nordgas, Stockholm, Sweden) and then to a three-way valve from which a timed collection (over 5 min) of a measured volume of gas could be made into a Douglas bag. The percentage of CO_2 in expired gas ($F\text{E}_{CO_2}$) was measured by the capnograph. Flow, volume and CO_2 signals were recorded using a u.v. recorder (S.E. Labs (EMI) Ltd, S.E. 3006). Volume was calibrated with a 50-ml syringe. The capnograph was calibrated using certified gas mixtures containing CO_2 within the measuring range. The deadspace of the system was 6 ml and the respiratory resistance of the system, pneumotachograph and in-line paediatric airway adaptor of the capnograph was 10 cm H_2O litre^{-1} s^{-1} with continuous flow rates up to 10 litre min^{-1}.

Calculations

$\dot{V}\text{E}$, $V\text{T}$, alveolar ventilation ($\dot{V}\text{A}$), deadspace volume per breath ($V\text{D}$) and carbon dioxide elimination ($\dot{V}CO_2$) were corrected to body temperature and pressure saturated (BTPS). The following formulae were used:

$$\dot{V}CO_2(\text{ml min}^{-1}) = \frac{\text{gas collection } \dot{V}\text{E} \times (F\bar{\text{E}}_{CO_2} - F\text{I}_{CO_2})}{100}$$

$$\dot{V}\text{A}(\text{ml min}^{-1}) = \frac{\dot{V}CO_2 \times 100}{\text{E}'_{CO_2} - \text{I}_{CO_2}}$$

$$V\text{D} = \frac{\dot{V}\text{E} - \dot{V}\text{A}}{f}$$

where $F\text{I}_{CO_2}$ is the fraction of CO_2 in inspired gas and I_{CO_2} is the mean inspired CO_2 concentration. During rebreathing the mean inspired CO_2 concentration was not known, therefore calculations of $\dot{V}\text{A}$ and $V\text{D}$ could not be made.

Evaluation of the clinical significance of rebreathing was made according to the criteria detailed by Kain and Nunn (1968) for evidence of alveolar rebreathing (see introduction and table III).

Plan of investigation

The anaesthetist in charge of the patient was not involved in the study, and was at liberty to control the depth of anaesthesia. No measurements were made until anaesthesia was considered clinically stable, the halothane concentration constant and at least 20 min had elapsed since induction.

Measurements of $\dot{V}\text{E}$, $V\text{T}$, $F\bar{\text{E}}_{CO_2}$, I_{CO_2}, E'_{CO_2}, arterial pressure and heart rate were then made with no rebreathing using a fresh gas flow (FGF) which was just great enough to avoid rebreathing (FGF_r). This borderline for rebreathing of CO_2 was determined in each patient by the use of the capnograph at gradually decreasing FGF. The FGF setting before the one during which CO_2 in inspired gas was first detected (FGF_r) was used during measurements at "no rebreathing".

Then, FGF was decreased to achieve a maximal inspired CO_2 concentration per breath ($\text{I}_{CO_2 max}$)(%) of about 1.5%. Measurements of $\dot{V}\text{E}$, $V\text{T}$, f, I_{CO_2}, E'_{CO_2}, arterial pressure and heart rate were obtained just before the change of FGF setting and then every minute during a 5-min

TABLE II. *Mean values ±1 SD for arterial pressure, heart rate and respiratory rate before (0), 2, 5 and 10 min of rebreathing or CO_2 inhalation*

	Rebreathing				CO_2 inhalation (min)			
	0	2	5	10	0	2	5	10
Arterial pressure (mm Hg)								
Systolic	101±18	96±9	97±11	96±12	97±19	92±13	95±11	95±10
Diastolic	53±17	48±7	49±9	49±9	52±16	47±10	49±7	50±8
Heart rate (beat min^{-1})	122±22	118±21	117±19	117±18	116±20	114±18	116±16	114±17
Respiratory rate (b.p.m.)	29±11	29±11	28±9	28±8	27±9	28±9	28±9	28±8

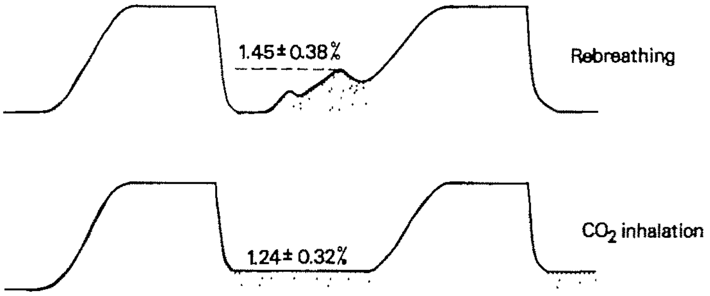

FIG. 2. The pattern of CO_2 during inspiration investigated in this study. Values are mean ± 1 SD $I_{CO_2,max}$ and mean I_{CO_2}.

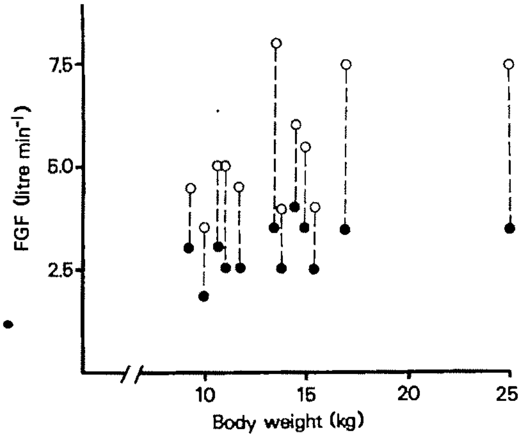

FIG. 3. The fresh gas flow (FGF) at borderline for rebreathing (open circles) and after reductions to low FGF (closed circles) in each patient indicated by body weight in kg.

period and finally after 10 min of rebreathing. FGF was then returned to its initial value (FGF_r).

After a further five minutes of "no rebreathing" at FGF_r, CO_2 was added to the inspired gas from CO_2 rotameters. A CO_2 inhalation slightly lower than $I_{CO_2,max}$, that is between 1.0 and 1.5% CO_2, was set during this part of the study. The chosen concentration of added CO_2 was somewhat lower than the maximum CO_2 concentration found during rebreathing so as to produce a CO_2 load similar to that during rebreathing. The same measurements as during rebreathing were then performed for up to 5 min and finally after 10 min. During the 5th and 10th minute of CO_2 inhalation samples of expired gas were collected for measurement of $F\bar{E}_{CO_2}$.

Statistics

Mean values and standard deviation (SD) were calculated. The results were evaluated by the use of paired *t* test applied to mean data.

RESULTS

Arterial pressure, and heart and respiratory rates were virtually unchanged during periods of rebreathing and CO_2 inhalation (table II). The two CO_2 exposures during inspiration are presented schematically in figure 2. The mean values (±1 SD) of $I_{CO_2,max}$ and of I_{CO_2} were $1.45 \pm 0.38\%$ and $1.24 \pm 0.32\%$ respectively.

Rebreathing

The $I_{CO_2,max}$ (%) given in figure 2 was achieved after the FGF_r had been decreased by 44% from (mean ± 1 SD) 5.25 ± 1.58 litre min^{-1} to 2.96 ± 0.59 litre min^{-1} ($P < 0.001$). Individual decreases in FGF are illustrated in figure 3 and ranged from 0.7 to 2.5 times the measured minute ventilation. The relationship between the $I_{CO_2,max}$ (%) and the $FGF/\dot{V}_E$ ratio was described by the regression equation: $I_{CO_2,max} = -0.71 . FGF/\dot{V}_E + 2.49$ with a coefficient of correlation of -0.79 (fig. 4).

There was considerable variation in response to this level of rebreathing. In no child did E'_{CO_2} increase significantly and in several no increases were seen in $\dot{V}_E$ and V_T (fig. 5). After 10 min of rebreathing mean $\dot{V}_E$ and V_T had increased by 18 and 24%, respectively (ns). Mean respiratory rate and E'_{CO_2} were unchanged (fig. 6).

Only one child fulfilled the criteria of Kain and Nunn for significant rebreathing (table III, fig. 10).

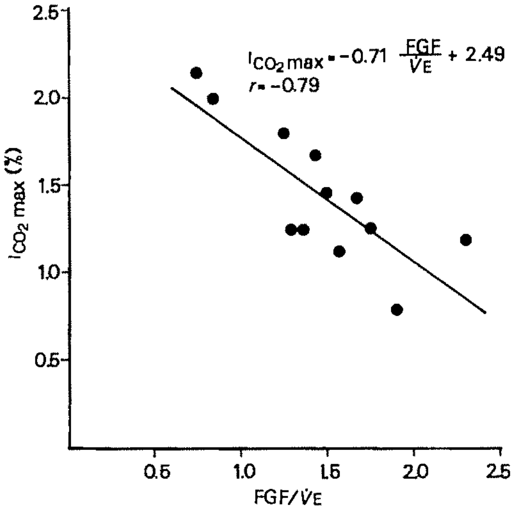

FIG. 4. The relationship between $I_{CO_2,max}$ (%) and FGF/$\dot{V}_E$ ratio in all 12 patients. Regression equation and coefficient of correlation are presented.

Inhalation of *carbon dioxide*

The ventilatory response to the inhalation of 1.24±0.32% carbon dioxide (mean±1 SD, fig. 2) was similar to that found during rebreathing at low FGF. The seven patients who responded to CO_2 did so within 2 min. In five patients there were no increases in $\dot{V}_E$ and V_T (fig. 7). E'_{CO_2} concentrations remained unchanged at this inspired CO_2 concentration. After 10 min of CO_2 inhalation mean values of $\dot{V}_E$ and V_T were increased by 18 and 19%, respectively. Respiratory rate and E'_{CO_2} were unchanged (fig. 8).

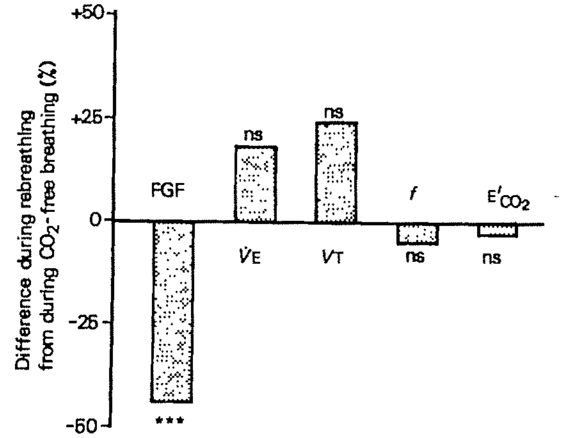

FIG. 6. Mean % difference in FGF, $\dot{V}_E$, V_T, f and E'_{CO_2} before and after 10 min of rebreathing an $I_{CO_2,max}$ of 1.45±0.38% (mean±1 SD).

Carbon dioxide elimination ($\dot{V}_{CO_2}$) was unchanged during the inhalation of carbon dioxide.

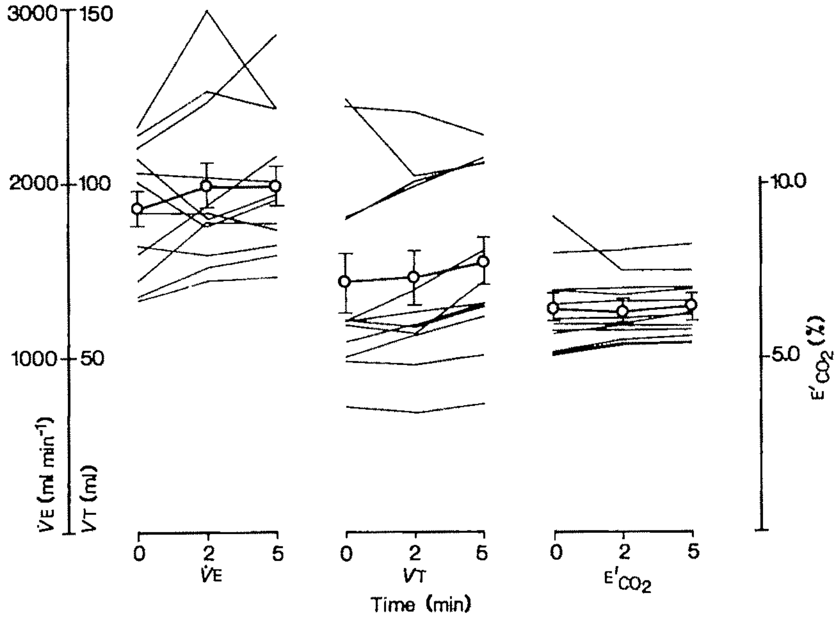

FIG. 5. Minute ventilation ($\dot{V}_E$), tidal volume (V_T) and end-tidal CO_2 concentration (E'_{CO_2}) in each patient before (0), and after 2 and 5 min of rebreathing at low fresh gas flows. Mean values (±SEM) are shown as open circles with vertical bars, and thick lines.

TABLE III. *Evaluation of rebreathing according to criteria for rebreathing set by Kain and Nunn (1968): I.* $\dot{V}_E > 10\%$, $P_{E'CO_2}$ *unchanged; II.* $\dot{V}_E$ *unchanged,* $P_{E'CO_2} > 0.7$ *kPa; III.* $\dot{V}_E > 5\%$, $P_{E'CO_2} > 0.3$ *kPa.* $P_{E'CO_2}$ *= end-tidal* CO_2 *tension (kPa).* FGF_r *= the fresh gas flow borderline for rebreathing and* FGF_{low} *= the low fresh gas flow at which rebreathing of about 1.5% occurred. + Indicates criterion fulfilled and 0 not fulfilled*

Patient No.	FGF_r FGF_{low}	$I_{CO_2,max}$ (%)	$\dot{V}_E$ change (%)	$P_{E_{CO_2}}$ change (kPa)	Criteria		
					I	II	III
1	7.5 3.5	1.67	+5.3	±0	0	0	0
2	7.5 3.5	1.80	+26	−1.6	0	0	0
3	6.0 4.0	1.19	+16	−0.13	0	0	0
4	3.7 2.5	1.45	+3.6	−0.27	0	0	0
5	5.0 2.5	2.15	+52	−0.98	0	0	0
6	3.5 1.8	2.0	+37	+0.20	+	0	0
7	4.5 2.5	1.24	+31	−0.28	0	0	0
8	4.0 2.5	1.44	+23	−0.32	0	0	0
9	5.5 3.5	1.11	−1	+0.13	0	0	0
10	4.5 3.0	0.79	−4	+0.07	0	0	0
11	5.0 3.0	1.25	±0	+0.46	0	0	0
12	8.0 3.5	1.25	+6	+0.17	0	0	0

This was achieved by a higher $\dot{V}_A$ which was increased by 32 % (mean value ± 1 SD) from 1212 ± 231 ml min^{-1} before to 1603 ± 450 ml min^{-1} during CO_2 inhalation ($P < 0.05$)(fig. 9). V_D/V_T ratios (mean ± 1 SD) decreased by 23 % from 0.31 ± 0.13 before to 0.24 ± 0.12 during CO_2 inhalation (ns) (fig. 9).

In spite of the inhalation of carbon dioxide (that is CO_2 present also early during inspiration), the criteria of Kain and Nunn for clinically significant rebreathing were fulfilled in only six of the 12 children (fig. 10).

DISCUSSION

At low fresh gas flows in anaesthetic systems such as Mapleson D, E and F (Willis, Pender and Mapleson, 1975) rebreathing appears late during inspiration. Therefore, apparatus and patient deadspaces could be the only parts exposed to inspired CO_2. Under these circumstances rebreathing would not create any CO_2 load as far as the patient is concerned. There are, however, difficulties in calculating the amount of CO_2 that reaches the alveoli so the clinical importance of

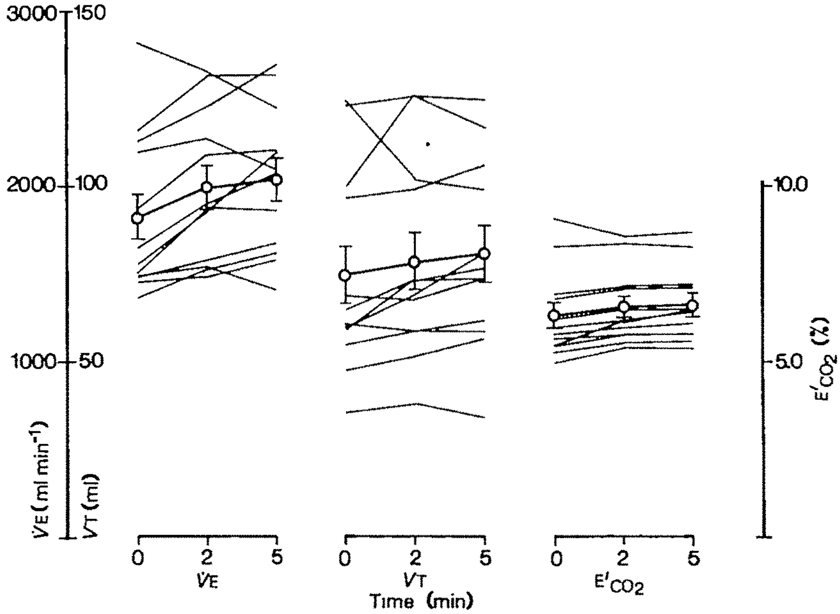

FIG. 7. Minute ventilation ($\dot{V}$E), tidal volume (VT) and end-tidal CO_2 concentration (E'$_{CO_2}$) in each patient before (0), and after 2 and 5 min of rebreathing at low fresh gas flows. Mean values (±SEM) are shown as open circles with vertical bars, and thick lines.

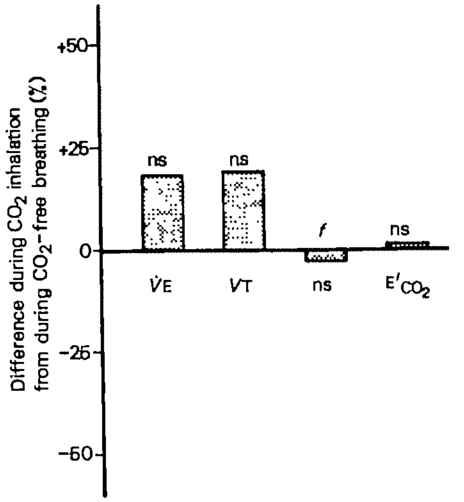

FIG. 8. Mean % difference in $\dot{V}$E, VT, f and E'$_{CO_2}$ before and after 10 min of inhalation of CO_2 at I_{CO_2} 1.24±0.32% (mean±1 SD).

rebreathing has still to be judged from ventilatory responses in patients, and criteria for the evaluation of ventilatory changes have been described by Kain and Nunn (1968).

At FGF/$\dot{V}$E ratios of 2 with spontaneous breathing in Mapleson D, E and F systems rebreathing is known to occur in most patients (Lindahl, Charlton and Hatch, 1984). According to the regression equation for $I_{CO_2\,max}$ in this study the level of rebreathing at 2 FGF/$\dot{V}$E would be 1.1% CO_2. In the study by Meakins and Coates (1983) however, rebreathing did not occur at 2 FGF/$\dot{V}$E. This discrepancy was somewhat surprising since their theoretical mathematical calculations were correctly based on measurements in anaesthetized young patients; but their FGF to $\dot{V}$E ratios were derived from the Engström and Herzog (1959) nomogram for $\dot{V}$E estimations—published in 1959 for the setting of artificial ventilation which gave minute ventilations which were 30–40% higher compared with calculations from a recently published regression equation for $\dot{V}$E in anaesthetized spontaneously breathing children (Lindahl, Hulse and Hatch, 1984). If lower $\dot{V}$E had been used by Meakins and Coates, it is likely that rebreathing would have occurred at higher FGF/$\dot{V}$E ratios.

When FGF was reduced by more than 40% from that precisely required to avoid rebreathing, statistically significant ventilatory changes were not found. One individual demonstrated a marked ventilatory response with an increase in $\dot{V}$E of over 50% at an $I_{CO_2\,max}$ of 2.15% CO_2, which was the highest seen in the sample, but, as the end-tidal CO_2 tension decreased by almost 1 kPa (patient

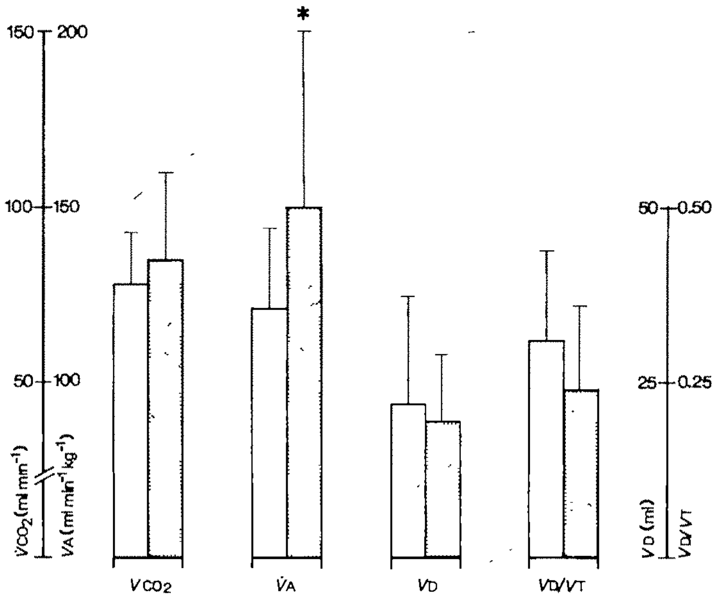

FIG. 9. Carbon dioxide output ($\dot{V}CO_2$), alveolar ventilation ($\dot{V}A$), deadspace volume (V_D) and V_D/V_T ratio before (unfilled columns) and after 10 min of 1.24±0.32% CO_2 inhalation (hatched columns).

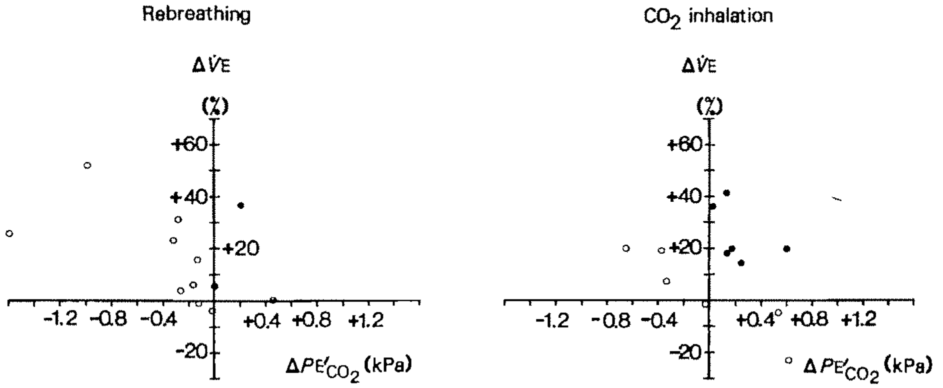

FIG. 10. Relations between measured changes of minute ventilation ($\Delta\dot{V}E$) in per cent and of end-tidal CO_2 tensions ($\Delta PE'_{CO_2}$) in kPa during rebreathing ($I_{CO_2,max}$: 1.45±0.38%, left diagram) and CO_2 inhalation (I_{CO_2}: 1.24±0.32%, right diagram). Filled circles represent children who did fulfil the criteria of rebreathing set by Kain and Nunn (1968), and open circles, those patients who did not.

No. 5, table III) Kain and Nunn's criteria for clinically important rebreathing were not fulfilled. Thus, it was difficult to find evidence of rebreathing within alveolar ventilation. As rebreathing occurs late in inspiration, the volume of rebreathed alveolar gas may stay within the deadspace and hence, not effect alveolar ventilation. Even so, rebreathing within alveolar gas has to be at least in the order of 1–1.25% CO_2 if a uniform ventilatory response was to be expected, since the ventilatory responses during CO_2 inhalation in this study were as variable as the responses during rebreathing. The six patients fulfilling the criteria during CO_2 inhalation were surprisingly few, as inhaled CO_2 always reaches the alveoli but were, on the other hand, sufficient to indicate that higher levels of alveolar CO_2 rebreathing cannot be accepted clinically.

The similarity in end-tidal carbon dioxide concentrations after 10 min of CO_2-free breathing, rebreathing or CO_2 inhalation suggests the presence of adequate compensatory respiratory mechanisms balancing CO_2 homeostasis in the body. The compensatory mechanisms during CO_2 inhalation did not primarily result in a uniform increase in minute ventilation. Alveolar ventilation was, however, increased ($P < 0.05$), indicating an adequate adaptation during CO_2 breathing at the depth of anaesthesia used in this study. An increased $\dot{V}$A that was explained most probably by the higher VT noted during CO_2 breathing (which is known to improve ventilation/perfusion ratio (Rose and Froese, 1980), that is to increase efficiency of ventilation) explained the unchanged E'_{CO_2} concentration before and during CO_2 inhalation found in this study.

To achieve a consistent response in $\dot{V}$E during rebreathing $I_{CO_2\,max}$ of 1.8% had to be reached, while lower concentrations resulted in variable responses (table III). According to the regression equation for the relationship between $I_{CO_2\,max}$ and FGF/$\dot{V}$E, FGF settings lower than $\dot{V}$E are likely to result in rebreathing within the alveolar ventilation. Such low fresh gas flows are at the utmost limit which can be tolerated in clinical practice using these breathing systems. During anaesthesia many things can go wrong; one of them being insufficient CO_2 elimination. Since, CO_2 is a factor which we know how to eliminate from inspired gas, fresh gas flows of at least 1.5 to 2 times $\dot{V}$E must be used to keep the maximal inspired CO_2 concentration within acceptable limits to achieve a necessary margin of safety in anaesthetized spontaneously breathing children. If the total elimination of rebreathing is desired, a fresh gas flow of 3.5 times $\dot{V}$E is required, according to the regression equation calculated in this study.

It was concluded that at an $I_{CO_2\,max}$ of $1.45 \pm 0.38\%$ resulting from low fresh gas flows, $\dot{V}$E increased by 18% (ns) and E'_{CO_2} was unchanged. Criteria for clinically important CO_2 rebreathing were only fulfilled in one patient. During the inhalation of $1.24 \pm 0.32\%$ CO_2, $\dot{V}$E was also increased by 18% (ns) and E'_{CO_2} was unchanged. Although, $\dot{V}$E did not increase significantly during the inhalation of $1.24 \pm 0.32\%$ CO_2, $\dot{V}$A did, indicating an intact and adequate ventilatory response to this level of CO_2 breathing during halothane anaesthesia. Estimations of $I_{CO_2\,max}$ could be made from the expression: $I_{CO_2\,max} = -0.7 \times FGF/\dot{V}E + 2.5$ and FGF to $\dot{V}$E ratios lower than 1 are likely to result in clinically significant rebreathing with $I_{CO_2\,max}$ concentrations of more than 1.8%. To avoid alveolar rebreathing, FGF settings of at least 1.5 to 2 times $\dot{V}$E must be used in these anaesthetic systems.

ACKNOWLEDGEMENTS

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VENTILATORY RESPONSES TO CARBON DIOXIDE IN CHILDREN DURING NITROUS OXIDE–HALOTHANE ANAESTHESIA

I. MURAT, M. CHAUSSAIN AND C. SAINT-MAURICE

SUMMARY

The ventilatory response to carbon dioxide was studied in 12 unpremedicated children, aged 20–68 months, weighing between 10 and 20 kg, under nitrous oxide–halothane anaesthesia. Tidal volume (VT) *and end-tidal carbon dioxide tension* (PE'_{CO_2}) *were continuously measured by pneumotachograph and capnograph. Minute ventilation* ($\dot{V}E$)*, respiratory rate* (f)*, mean inspiratory flow* ($\dot{V}I$) *and effective inspiratory cycle* (TI/T^{tot}) *were calculated during anaesthesia at three different inspired halothane concentrations* (0.5, 1 *and* 1.5%)*. The ventilatory response to carbon dioxide was determined by relating the increase in ventilation during exposure to 2% carbon dioxide to the change in end-tidal carbon dioxide concentration. When the inspired concentration of halothane increased, there were significant decreases in* $\dot{V}E$, VT, $\dot{V}I$, *and a significant increase in* PE'_{CO_2}. *The slope of the carbon dioxide response under light nitrous oxide–halothane anaesthesia* (0.5% *halothane*) *was relatively flat* ($18.64\ ml\ min^{-1}\ kg^{-1}\ mm\ Hg^{-1}$) *when compared with the mean values published for anaesthetized adults, children or neonates. When the inspired concentration of halothane was increased, the slope decreased significantly* (39% *of initial value at* 1% *inspired halothane,* 26% *at* 1.5%)*. The addition of carbon dioxide produced significant increases in* $\dot{V}E$, VT *and* $\dot{V}I$ *but no change in respiratory rate. No statistical difference was observed in the slope of carbon dioxide response between the initial and "control" periods which were measured at the same inspired halothane concentration* (0.5%)*.*

The effect of halothane on the ventilatory responses to carbon dioxide has been quantified in animals (Brandstater, Eger and Edelist, 1965; Ngai, Katz and Farhie, 1965; Weiskoff, Raymond and Severinghaus, 1974; Hirshman et al., 1977) and in unmedicated human subjects (Devine, Hamilton and Pittinger, 1958; Knill and Gelb, 1978; Tusiewicz, Bryan and Froese, 1977), and in both there was a progressive depression of the ventilatory response as the alveolar concentration of halothane was increased. Halothane is the most commonly used anaesthetic agent in paediatric anaesthesia (Reynolds, 1962; Krivosic-Horber, Sauvage and Calmes, 1973; Govaerts and Sanders, 1975); however, carbon dioxide sensitivity has never been studied in young children during general anaesthesia. This study was performed to assess the changes in alveolar ventilation and in the ventilatory response to carbon dioxide which were produced by increasing inspired halothane concentrations during nitrous oxide–halothane anaesthesia in children weighing between 10 and 20 kg.

PATIENTS AND METHODS

The ventilatory response to carbon dioxide was studied in 12 children scheduled for elective abdominal or genito-urinary surgery. The mean values (±SD) for age were 39±17 months (range 20–68 months), weight 15±2.9 kg (range

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10.5–20 kg) and height 96 ± 11.5 cm (range 77–111 cm) (table I). All patients were healthy, were taking no medication and had normal cardiopulmonary function. Parental consent was obtained before anaesthesia in each case after a full explanation. None of the children included in this study was premedicated. The study was performed either during the immediate preoperative stage (eight children) or during the postoperative period (four children) if no anaesthetic other than halothane and nitrous oxide had been used during the surgical procedure. In the four children in whom the study was carried out in the postoperative period, the surgical procedure (repair of hernia) lasted less than 15 min. Rectal temperature was monitored and maintained between 36.5 and 37.5 °C in all the children. ECG and arterial pressure were monitored continuously.

Anaesthesia was induced with oxygen and nitrous oxide in equal parts ($F\text{I}_{\text{O}_2}$ 0.5) and 2–2.5% halothane using an appropriate face mask and an open circuit with a non-rebreathing valve with a low opening pressure. Intubation of the trachea was performed without neuromuscular blockade under an appropriate inspired concentration of halothane with an uncuffed tracheal tube. After intubation, the inspired concentration of halothane was decreased to 0.5% and the children allowed to breathe spontaneously. The same calibrated vaporizer was used for all the children (Fluotec III). The fresh gas flow was identical for all patients (oxygen 4 litre, nitrous oxide 4 litre) throughout the study and sufficient to avoid rebreathing (Lindhal, Hulse and Hatch, 1984).

Tidal volume ($V\text{T}$) was measured by electronic integration of the flow signal obtained from a Fleisch No. 0 heated pneumotachograph (internal volume 4.7 ml) connected to a Godart differential pressure transducer. The flow signal was calibrated with room air using the Godart gas-flow calibration set. The tidal volume signal was calibrated with room air using syringes of known volume before and after each study. The pneumotachograph was inserted between the non-rebreathing valve and the tracheal tube. Carbon dioxide in the expired gas (E'_{CO_2}) was monitored continuously by direct sampling from the intratracheal tube to a capnograph with automatic correction for nitrous oxide (Datex). The rate of sampling was 50 ml min^{-1}. Flow and volume signals were recorded continuously on a two-channel Gould recorder.

After baseline ventilatory measurements had

TABLE I. *Individual values for age, height, weight and respiratory variables at the initial period of the study (T°). * Children studied after operation*

Child No.	Age (months)	Height (cm)	Weight (kg)	$P\text{E}'_{\text{CO}_2}$ (mmHg)	$\dot{V}\text{E}$ (ml min^{-1} kg^{-1})	$V\text{T}$ (ml kg^{-1})	f (b.p.m.)	$\dot{V}\text{I}$ (ml min^{-1} kg^{-1})	$T\text{I}/T^{\text{tot}}$	$\Delta\dot{V}\text{E}/\Delta P\text{E}'_{\text{CO}_2}$ (ml min^{-1} kg^{-1} kPa^{-1})
1	45	98	17	35.6	165.2	7.2	23	275	0.60	22
2*	68	111	19	45.6	119.6	5.26	22.7	221	0.54	16.9
3	23	84	11.8	38.5	142.3	4.31	33	356	0.40	9.1
4	36	88	14	32.8	151.4	2.8	53	261	0.58	16.5
5*	38	98	15.7	34.2	149.5	3.8	39.3	293	0.51	19.1
6	59	110	20	42	125.7	4.1	30.7	233	0.54	7.2
7	66	104	15	40.6	156.6	6.84	22.9	250	0.63	13.7
8	34	100	13	30.6	189.5	5.41	35	337	0.56	28.4
9	47	104	18	46.3	105.0	4.24	24.7	214	0.49	13.6
10*	34	102	16	39.9	153.8	4.76	32.3	280	0.55	15.1
11	20	77	10.5	34.7	173.5	5.51	31.4	309	0.56	16.4
12*	20	79	13	39.9	146.5	5.6	26	244	0.60	45.7

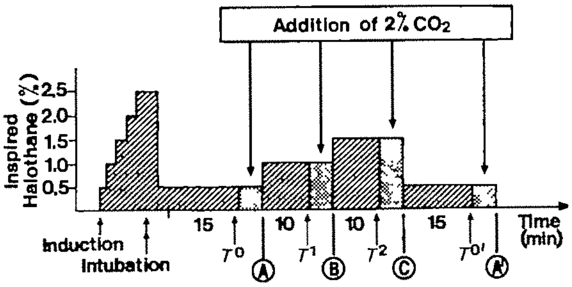

FIG. 1. Timing of the study. Baseline measurements were performed at T^0, T^1, T^2, $T^{0\prime}$. Measurements for ventilatory response to carbon dioxide were performed at A, B, C and A′.

been obtained at a selected inspired concentration of halothane, carbon dioxide was added to the inspired gas mixture so as to produce a constant inspiratory carbon dioxide concentration of 2% (controlled by the capnograph). This value was chosen in order to produce a moderate increase in $P\text{E}'_{\text{CO}_2}$ in the physiological range. After 5 min at a given inspired carbon dioxide concentration, the patient was considered to be in a steady-state and measurements of ventilation were undertaken at this time, although in all patients the respiratory variables were stable within 2 min of achieving the desired inspired concentration of carbon dioxide.

The ventilatory response to carbon dioxide was studied at three increasing inspired concentrations of halothane: 0.5, 1 and 1.5%. Baseline values of $V\text{T}$ and E'_{CO_2} were not recorded until 10 min after each change in the inspired concentration of halothane in order to obtain a stable alveolar concentration of halothane (fig. 1). After each study of carbon dioxide sensitivity, the added carbon dioxide was discontinued, before the inspired halothane concentration was increased. Finally, the inspired halothane concentration was decreased to 0.5% for 15 min and the response to carbon dioxide assessed again. This last period ($T^{0\prime}$), called "control period" was included for all of the children except one in order to determine any inter-patient variability and the eventual consequences of prolonged anaesthesia. The children were not stimulated in any way during the period of study.

At each inspired halothane concentration, the durations of inspiration ($T\text{I}$), expiration ($T\text{E}$) and total breathing cycle (T^{tot}) were measured from the flow signal by averaging 10 successive breaths.

The following respiratory variables were calculated: minute ventilation ($\dot{V}\text{E}$) (ml min^{-1} kg^{-1}), respiratory frequency (f), mean inspiratory flow ($\dot{V}\text{I}$) (ml min^{-1} kg^{-1}), effective inspiratory cycle ($T\text{I}/T^{\text{tot}}$) and end-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$) (kPa).

At each inspired halothane concentration, the slope of $\Delta\dot{V}\text{E}/\Delta P\text{E}'_{\text{CO}_2}$ (ml min^{-1} kg^{-1} mm Hg^{-1}) was used to express the sensitivity to carbon dioxide.

Statistical evaluation of the data was by one-way analysis of variance between the four periods of the study. At each inspired halothane concentration, comparisons of mean values before and after the addition of carbon dioxide were obtained using the t test for paired samples. P values of 0.05 or less were regarded as significant. The values are expressed as mean ± standard error of the mean (SEM).

RESULTS

The mean values of $P\text{E}'_{\text{CO}_2}$, $\dot{V}\text{E}$, $V\text{T}$, f, $\dot{V}\text{I}$ and $T\text{I}/T^{\text{tot}}$ for each inspired halothane concentration studied, before and after the addition of carbon dioxide, are shown in table II. There were no statistically significant differences ($P > 0.5$ for all variables) between the values recorded in the eight children studied before operation and those recorded in the postoperative period in four children (table I). Before the addition of carbon dioxide, there was a significant decrease in $\dot{V}\text{E}$ when the inspired concentration of halothane was increased, attributable, in the main, to a significant decrease in $V\text{T}$. The mean inspiratory flow decreased significantly also. The increase in respiratory rate was significant between 1 and 1.5% inspired halothane and between 0.5 and 1.5%. Changes in $P\text{E}'_{\text{CO}_2}$ were also related to changes in inspired halothane concentration. When compared with T^0, the period $T^{0\prime}$ was marked by a significant decrease in $T\text{I}/T^{\text{tot}}$ and an increase in $P\text{E}'_{\text{CO}_2}$, although there were no significant changes in $\dot{V}\text{E}$, $V\text{T}$ or respiratory rate.

The mean results for the slope of the carbon dioxide response at increasing inspired halothane concentrations are shown in table II. There was a significant decrease in the slope as the inspired halothane concentration increased. The mean value for the slope at T^1 was 39% of the initial value at T^0 ($P < 0.01$) and 26% at T^2 ($P < 0.001$). On the other hand, no statistical difference was observed in the slope when the initial and control periods, which were measured at the same inspired halothane concentration (0.5%), were compared. At each inspired halothane concentration, the values of the respiratory variables were compared

TABLE II. *Mean values* ($\pm$*SEM*) *for* $P\acute{E}_{CO_2}$ (*kPa*), $\dot{V}E$ (*ml* min^{-1} kg^{-1}), VT (*ml* kg^{-1}), f, TI/T^{tot}, $\dot{V}I$ (*ml* min^{-1} kg^{-1}) *before and after addition of carbon dioxide at different inspired concentration of halothane.* † *Significant changes of inspiratory parameters at* $FI_{CO_2} = 0$ *when compared with the initial value at* T°; * *significant changes of respiratory parameters before and after addition of carbon dioxide at the same inspired concentration of halothane* (*t test for paired samples*): † *or* *$P < 0.05$; ††$P < 0.01$; ††† *or* *** $P < 0.001$. *Mean values* ($\pm$*SEM*) *for slope of ventilatory response to carbon dioxide* ($\Delta\dot{V}E/\Delta P\acute{E}_{CO_2}$ *ml* min^{-1} kg^{-1} *mm* Hg^{-1}) *are compared with values at* T°

	Inspired halothane concentration (%)											
	0.5			1			1.5			0.5 (control)		
FI_{CO_2}:	0		0.02	0		0.02	0		0.02	0		0.02
$P\acute{E}_{CO_2}$ (mm Hg)	38.4 ±1.43	***	40.7 ±1.38	†††40.8 ±1.63	***	44.6 ±1.53	†††45.9 ±1.74	***	50.2 ±1.60	††40.0 ±1.42	***	42.5 ±1.51
$\dot{V}E$ (ml min^{-1} kg^{-1})	148.2 ±6.7	***	189.2 ±10.3	†††129.9 ±7.8	***	155.9 ±9	†††113.4 ±6	***	133.1 ±9	140.8 ±6.8	***	175.8 ±10.2
VT (ml kg^{-1})	4.98 ±0.36	***	6.48 ±0.47	†††4.11 ±0.29	***	4.93 ±0.37	†††3.34 ±0.25	***	3.95 ±0.30	5.06 ±0.34	***	6.24 ±0.45
f (b.p.m.)	31.2 ±2.5		30.2 ±2.1	32.7 ±2.4		32.9 ±2.4	†††35.4 ±2.7		35.2 ±2.7	28.8 ±1.9		28.9 ±1.9
$\dot{V}I$ (ml min^{-1} kg^{-1})	272.7 ±12.9	***	339.2 ±17.9	†††243.4 ±14.4	***	285 ±15.3	†††217.7 ±11.6	***	251.7 ±16.2	262.5 ±13	***	319.9 ±18.7
TI/T^{tot}	0.55 ±0.02		0.56 ±0.02	0.53 ±0.02	*	0.55 ±0.02	†0.52 ±0.01		0.53 ±0.02	††0.54 ±0.02		0.55 ±0.02
$\Delta\dot{V}E/\Delta P\acute{E}_{CO_2}$ (ml min^{-1} kg^{-1} mm Hg^{-1})		18.64 ±2.93			††7.27 ±2.10			†††4.84 ±1.40			15.50 ±1.65	

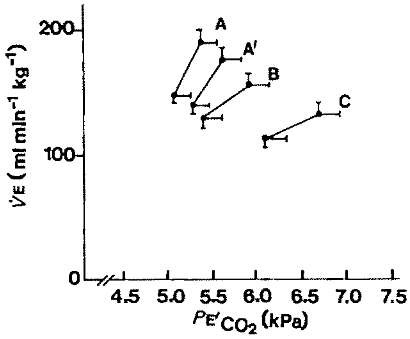

FIG. 2. Changes in $\dot{V}\text{E}$ (± SEM) related to changes in $P\text{E}'_{\text{CO}_2}$ (± SEM) during exposure to 2% carbon dioxide. Inspired halothane concentrations: 0.5%(A), 1%(B), 1.5%(C) and 0.5%(control) (A′) (applies to figures 3, 4 also).

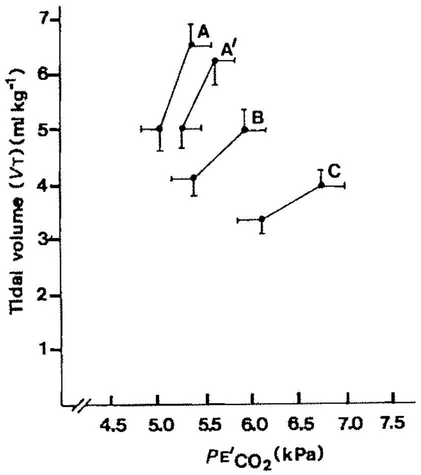

FIG. 3. Changes in $V\text{T}$ related to changes in $P\text{E}'\text{CO}_2$ during exposure to 2% carbon dioxide.

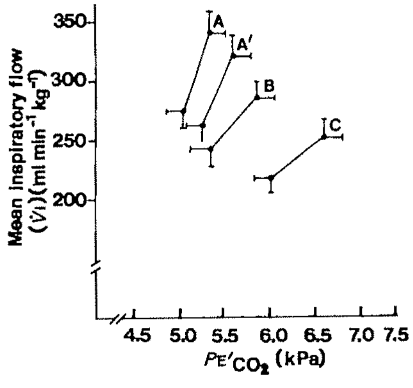

FIG. 4. Changes in $\dot{V}\text{I}$ related to changes in $P\text{E}'_{\text{CO}_2}$ during exposure to 2% carbon dioxide.

with the initial values before the addition of carbon dioxide. The addition of carbon dioxide produced a significant increase in $P\text{E}'_{\text{CO}_2}$, and a significant increase in $\dot{V}\text{E}$ ($P < 0.001$ at each period) as a result of a significant increase in $V\text{T}$ ($P < 0.001$ at each period), but the respiratory rate did not change significantly. Carbon dioxide produced a significant increase in mean inspiratory flow ($P < 0.001$ at each period). Changes in $\dot{V}\text{E}$, $V\text{T}$ and $\dot{V}\text{I}$ during exposure to 2% carbon dioxide related to change in $P\text{E}'_{\text{CO}_2}$ are shown in figures 2, 3 and 4.

DISCUSSION

Effects of halothane on ventilation

The increases in inspired halothane concentration produced a significant decrease in $\dot{V}\text{E}$, for the main part as a result of a marked decrease in $V\text{T}$. There was also a significant decrease in mean inspiratory flow and a significant increase in $P\text{E}'_{\text{CO}_2}$. Thus, the increase in the inspired halothane concentration produced, as previously reported in adults, a marked decrease in alveolar ventilation. The decreases in tidal volume and mean inspiratory flow seem to result from a central action of halothane as previously demonstrated by Ngai, Katz and Farhie (1965). Significant changes in respiratory rate did not occur in children, but the decrease in tidal volume was more marked than in the adult; similar results were previously reported by Wilson and Harrison (1964). The high chest-wall compliance in children produces a relative ineffectiveness of the ribcage in generating volume changes during anaesthesia (Nunn and Ezi-Ashi, 1961; Tusiewicz, Bryan and Froese 1977). During the control period, there was a significant decrease in inspiratory duty cycle and a significant increase in $P\text{E}'_{\text{CO}_2}$, when compared with the initial period. These changes may be the result of a direct effect of halothane on inspiratory muscles with progressive recovery (Nishino et al., 1984).

Effects of halothane on ventilatory response to CO$_2$

Mean values for the slope of the carbon dioxide response at the initial period (halothane concentration 0.5%) were much lower than the values published for awake adults by Read (1967) and Knill and Gelb (1978) and for awake children by Chaussain and colleagues (1977) and Tusiewicz, Bryan and Froese (1977). The mean slope in children weighing 25–56 kg and aged 8–15 yr, is 63 ml min^{-1} kg^{-1} mm Hg^{-1}. Our values measured during the initial period were also lower than normal values reported by Davi and co-workers (1979) for unanaesthetized full-term neonates (45 ml min^{-1} kg^{-1} mm Hg^{-1}). Data concerning normal values of carbon dioxide response in young children are lacking but, using the information available, our results demonstrate that, during light general anaesthesia with nitrous oxide and 0.5% halothane, sensitivity to carbon dioxide is decreased markedly.

When the inspired halothane concentration was increased, there was a significant decrease in the ventilatory response to carbon dioxide and the curves were shifted to the right. These results are in agreement with data in man previously published by Knill and Gelb (1978). These authors reported that the ventilatory response to carbon dioxide was unchanged between the awake state and the inspiration of halothane at 0.1 MAC. At 1.1 MAC, the mean slope of the response to carbon dioxide was 38% of the awake slope; at 2 MAC, it was only 17% of the control value. Changes in carbon dioxide responsiveness at various depths of anaesthesia are caused by the direct effect of halothane on the central regulatory and integratory mechanisms (Ngai, Katz and Farhie, 1965). In our study, when the inspired halothane concentration increased, the carbon dioxide response was markedly decreased, but not abolished. During halothane anaesthesia, the carbon dioxide response is not changed by hyperoxia (Duffin, Triscott and Whitwam, 1976; Knill and Gelb, 1978) which probably occurred during our study, in which children were breathing a constant mixture of 50% oxygen. The MAC fraction of nitrous oxide is additive to the MAC fraction of halothane and the effects of nitrous oxide on the respiratory pattern of spontaneously breathing children during halothane anaesthesia have been reported recently by Wren and colleagues (1984). Nitrous oxide produced decreases in $\dot{V}\mathrm{E}$, $V\mathrm{T}$ and an increase in $P\mathrm{E}'_{CO_2}$ without change in inspiratory rate, but had little effect on the ventilatory response to carbon dioxide (Hornbein et al., 1969). However, a mixture of nitrous oxide and oxygen is generally used during halothane anaesthesia and this study was essentially performed to assess real changes in the carbon dioxide response under general anaesthesia with nitrous oxide and halothane in children. The MAC value for halothane in children aged 2.5–6 yr is 0.91 (Gregory, Eger and Munson, 1969). The MAC fractions obtained in our study during nitrous oxide–halothane anaesthesia were calculated as 0.8 at T^0, 1.1 at T^1 and 1.4 at T^2—values which are used widely in current clinical practice.

At each inspired halothane concentration, the addition of carbon dioxide produced significant increases in both $P\mathrm{E}'_{CO_2}$ and $\dot{V}\mathrm{E}$. The increase in $\dot{V}\mathrm{E}$ was the result of the increase in $V\mathrm{T}$, as the respiratory rate did not change. In unanaesthetized infants aged between 2 weeks and 4 months, Haddad and co-workers (1980) found, as we did, an increase in tidal volume of up to 45% and no change in respiratory frequency during the inhalation of 2% carbon dioxide. Inhalation of carbon dioxide also produced a marked increase in mean inspiratory flow, which reflected a more rapid increase in centrally generated respiratory activity, which tends to decrease $T\mathrm{I}$. In adult subjects anaesthetized with halothane, Higgs and Carli (1983) reported, as in our study, an increase in driving pressure and inspiratory flow. However, they have also shown, unlike us, an increase in respiratory rate in response to the increase in inspired carbon dioxide concentration.

The control period was studied in order to assess the individual variability in carbon dioxide response, and the effect of the duration of anaesthesia. The lack of significant change in the slope between the initial period and the control period (at the same inspired halothane concentration) is in agreement with that previously reported in 1965 by Brandstater, Eger and Edelist. These authors demonstrated that, in dogs at a constant alveolar halothane concentration, the ventilatory response to carbon dioxide remained essentially unchanged for up to 8 h and that a slight change in base line $P\mathrm{E}'_{CO_2}$ did not affect this response.

The decrease in carbon dioxide sensitivity in children during nitrous oxide–halothane anaesthesia reported in this study, is an important reason for closely monitoring children under general anaesthesia so as to avoid any additional factors responsible for interference with the maintenance of adequate ventilation.

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ATTEMPTED ACCELERATION OF THE ONSET OF ACTION OF PANCURONIUM*

Effects of Divided Doses in Infants and Children

J. C. BEVAN, F. DONATI AND D. R. BEVAN

SUMMARY

The study was designed to determine whether the onset of action of pancuronium in infants and children could be accelerated by its administration in divided doses. Sixty paediatric patients (0–1 yr (n = 20); 1–3 yr (n = 20); 3–10 yr (n = 20)) were studied during nitrous oxide–oxygen–halothane anaesthesia using train-of-four stimulation, and the results were compared with data obtained previously in adults. The time to onset correlated with the patient's age, and an additional, small acceleration was produced following divided doses which did not alter the duration or pattern of neuromuscular blockade. It was concluded that, in children, divided doses of pancuronium are unlikely to offer important clinical advantages.

Since arterial oxygen tension decreases rapidly during apnoea (Weitzner, King and Ikezono, 1959), neuromuscular blocking drugs should have a rapid onset of action when used to facilitate tracheal intubation. This is particularly important in infants and children, since, in these patients, Pa_{O_2} may decrease more rapidly as a result of an increasing oxygen consumption, restlessness makes pre-oxygenation difficult, and the anatomy impedes intubation.

It has been observed recently that a small dose of a non-depolarizing neuromuscular blocking drug accelerates the onset of subsequent doses of the same drug. This has been reported in adults after divided doses of alcuronium (Hutton et al., 1983), atracurium (Gergis et al., 1983; Nagashima, Nguyen et al., 1984), pancuronium (Doherty et al., 1985) and vecuronium (Foldes et al., 1984). Also, surgical relaxation was hastened when pancuronium was preceded by a small "priming" dose of metocurine (Nagashima, Stoll et al., 1984).

Comparisons of the different behaviour of neuromuscular blockers in children and adults are difficult because of different methodology and anaesthesia. Nevertheless, it seems that the onset of action of non-depolarizing drugs is more rapid in children than in adults and this is said to be a consequence of more rapid drug delivery to the muscles in the very young. Despite the problems of different methodology, the more rapid onset of action has been demonstrated clearly using equipotent doses of vecuronium (Fisher and Miller, 1983).

The present study was designed to complement a previous investigation in adults in which the same anaesthetic technique, dose of myoneural blocker and neuromuscular monitoring were used (Doherty et al., 1985). The aim was to determine whether the onset of action and duration of effect of pancuronium were modified by its administration in divided doses to infants and children from 0 to 10 years of age.

PATIENTS AND METHODS

The procedure was approved by the Hospital Committee on Medical and Dental Evaluation. Sixty infants and children were studied during various surgical procedures of at least 1 h duration. No patients with hepatic, renal or neuromuscular disease, any electrolyte abnormality, or who were receiving drugs known to

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interfere with neuromuscular transmission were included. Patients were studied in three groups of 20, according to age. Group 1 consisted of "infants" aged less than 12 months. Groups 2 and 3 consisted of "young children" aged from 1 to 3 yr and "older children" from 3 to 10 yr, respectively. Each group was subdivided randomly into two subgroups of 10 patients to receive pancuronium either as a single dose of 0.07 mg kg^{-1} or as an initial (10%) dose of 0.007 mg kg^{-1} 3 min before the main dose of 0.063 mg kg^{-1}.

Premedication for all infants consisted of hyoscine 0.01 mg kg^{-1} i.m. The children received pentobarbitone 3 mg kg^{-1} rectally 2 h before surgery, followed by morphine 0.1 mg kg^{-1}, and hyoscine 0.01 mg kg^{-1} i.m. 1 h before surgery. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 2–3 μg kg^{-1} i.v., and maintained with 70% nitrous oxide and 0.5–1% halothane (inspired concentration) in oxygen. Endotracheal intubation was performed after the administration of the larger dose of pancuronium and ventilation was controlled to maintain normocarbia using the Bain system. Fresh gas flows were set according to the recommendations of Rose and Froese (1979) and, in most subjects, end-tidal $P\text{CO}_2$ was measured with a Hewlett-Packard capnograph to maintain $P\text{E}'_{\text{CO}_2}$ at 4–5 kPa. Oesophageal temperature was measured and maintained between 35.5 and 37 °C. Neuromuscular transmission was monitored as described by Ali, Utting and Gray (1970). The ulnar nerve was stimulated supramaximally using silver–silver chloride electrodes applied to the forearm. Trains of four square pulses of 0.2 ms duration at a frequency of 2 Hz were repeated every 12 s using a Grass S48 stimulator and an SIU5 isolation unit. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis was measured with a force displacement transducer (Grass FT03) and recorded using a pen-and-ink recorder (Grass Polygraph). Neuromuscular blockade was expressed as the height of the first twitch (T1) as a percentage of pre-drug control values, and as the train-of-four ratio (T4/T1) (the height of the fourth twitch divided by the height of the first in each train). Pancuronium was not administered until the twitch recovery had stabilized, which usually occurred within 5–10 min.

The speed of onset of neuromuscular blockade was estimated as the time from the injection of the bolus or larger dose of pancuronium to 50% and 90% depression of T1, and the duration of action was assessed as the time from injection until T1 had recovered to 10%. Train-of-four ratios were measured at 10% decrements of T1 during the onset of blockade. These results in infants and children have been compared with those obtained in adults in a recent study using similar methodology (Doherty et al., 1985).

Results are presented as mean values with standard error of the mean (SEM) as an index of dispersion. Where applicable, mean values were compared using one-way analysis of variance and unpaired Student's t test with Bonferoni's modification (Glantz, 1981). Regression lines were constructed using the method of least squares and Kendall–Rank (KR) correlation coefficients were calculated.

RESULTS

At each age group the subgroups were comparable with respect to age and weight (table I).

Onset and recovery of neuromuscular blockade

The onset times to 50 and 90% block of T1 are shown in table II. Blockade developed more rapidly in the young and there were significant correlations between the patient's age and the times to 50 and 90% block ($P < 0.001$, KR). The onset tended to be more rapid when pancuronium was administered in divided doses, but this reached statistical significance only in the development of 50% block in the 3–10 yr group.

TABLE I. *Age and weights of patients studied*

	Single dose			Divided dose		
Group	*n*	Age (month)	Weight (kg)	*n*	Age (month)	Weight (kg)
Infants	10	6.5±1.2	7.4±0.7	10	5.4±1.3	7.5±0.8
Young children	10	24.1±2.8	10.8±1.6	10	24.0±2.1	12.5±1.3
Older children	10	61.8±6.2	19.8±2.8	10	58.5±3.3	18.8±1.1

TABLE II. *Onset and recovery data for the three paediatric groups compared with a previous adult study* (Doherty et al., 1985). Numbers in parentheses = n*

Age	Single dose	Divided dose	*P*
Time to 50% block (min)			
0–1 yr	0.8±0.1 (10)	0.7±0.1 (10)	ns
1–3 yr	1.2±0.1 (10)	0.9±0.1 (10)	ns
3–10 yr	1.5±0.2 (10)	1.1±0.1 (10)	<0.05
Adult*	1.9±0.1 (29)	1.2±0.1 (23)	<0.001
Time to 90% block (min)			
0–1 yr	1.3±0.2 (10)	1.1±0.1 (10)	ns
1–3 yr	2.1±0.3 (10)	1.6±0.3 (10)	ns
3–10 yr	2.7±0.4 (10)	1.6±0.2 (8)	ns
Adult*	3.4±0.4 (29)	2.1±0.1 (23)	<0.01
Time to 10% recovery (min)			
0–1 yr	30.0±2.4 (6)	26.8±2.9 (10)	ns
1–3 yr	25.0±2.0 (10)	28.7±4.0 (10)	ns
3–10 yr	25.9±3.4 (10)	28.4±3.8 (8)	ns
Adult*	45.9±2.9 (29)	57.1±4.3 (23)	<0.05

TABLE III. *Train-of-four ratios during onset of neuromuscular block after pancuronium given as single or divided doses*

	Single dose			Divided dose		
T1	0–1 yr	1–3 yr	3–10 yr	0–1 yr	1–3 yr	3–10 yr
70%	78.3±2.2	73.6±2.3	67.6±3.0	76.8±1.7	70.0±2.8	72.3±2.9
50%	67.9±1.8	64.7±2.6	56.6±4.6	69.7±1.5	59.4±2.1	57.9±4.6
30%	56.7±2.3	55.6±3.9	41.6±4.5	58.3±2.4	47.8±2.1	44.7±4.8

The durations of blockade were similar in all paediatric groups, and were not affected by giving pancuronium in divided doses.

Compared with previous adult data, the onset of neuromuscular blockade was more rapid in children and, although there was a tendency towards acceleration of the block when the drug was administered in divided doses, the effect was small and seldom achieved statistical significance. The duration of action was shorter in children than in adults, but did not demonstrate any difference between single and divided doses.

Pattern of neuromuscular blockade

The relationship between T1 depression and T4/T1 ratio was similar to that previously described in paediatric patients following bolus doses of pancuronium (Robbins et al., 1984). Following the single dose of pancuronium, T4/T1 ratio tended to decrease in the older children. When T1 was decreased by 30% and 70%, the T4/T1 ratio was significantly less in the older children than in infants. No differences were observed in T4/T1 ratios between the groups who had received single or divided doses of pancuronium (table III).

DISCUSSION

It is important to search for ways to accelerate the onset of action of non-depolarizing neuromuscular blockade because the use of suxamethonium to facilitate rapid intubation of the trachea is not always indicated or desirable. This study showed a decrease in the onset time for pancuronium in younger patients and, even in the older age group studied (3–10 yr), the onset was more rapid than in adults (Doherty et al., 1985). However, the ideal neuromuscular blocker should have a much shorter onset of action in infants because their relatively greater oxygen consumption predisposes to arterial hypoxaemia (Kaplan and Graves, 1984). Although pre-oxygenation can delay the onset of hypoxaemia in adults (Weitzner, King and Ikezono, 1959), the protection afforded by such a manoeuvre in a young, unco-operative patient has not been evaluated.

Some acceleration in the onset of neuromuscular blockade was achieved by administering pancuronium in divided doses. However, the effect was small and much less than that seen previously in adults, although the magnitude and timing of the divided doses were similar (Doherty et al., 1985). The small priming dose of pancuronium was chosen to avoid serious muscle weakness. Indeed, such doses of blockers seldom produce more than small decreases of neuromuscular activity without effect on ventilation (Ferguson and Bevan, 1981; Gal and Goldberg, 1981). Similarly, the interval of 3 min between the priming and the main dose of pancuronium was selected because this is sufficient to avoid the problems associated with suxamethonium when tubocurarine is used for "pre-curarization" (Horrow and Lambert, 1984). However, Foldes has recommended larger priming doses (pancuronium 0.015–0.02 mg kg^{-1}) followed, 6–8 min later, by the intubating dose (Foldes, 1984). Priming doses of this magnitude can be expected to produce measurable weakness.

Several reasons can account for the acceleration of the onset of neuromuscular blockade when blockers are administered in divided doses. Paton and Waud (1967) have demonstrated that at least 70% of post-junctional receptors need to be occupied by neuromuscular blocking agents before neuromuscular transmission is measurably impaired. This concept, which they called the "margin of safety", has been confirmed by direct measurement of receptor occupation by blocking drugs (Caratsch et al., 1979). Consequently, the small priming doses of neuromuscular blocker used in the present study produced occupation of receptors without paralysis. When a second paralysing dose of drug was given the remaining proportion of unoccupied receptors needed only to have a small number occupied to produce paralysis. Also, if calculations are made to predict the time taken for the concentration of blocking drug at the "effect" compartment (biophase) (Hull et al., 1978) to reach paralysing values, then this can account for an acceleration of about 0.2 min (Doherty et al., 1985), which is compatible with the results in the present study.

When "priming" doses are given with a drug different from the "intubating" dose, additional acceleration may occur if the two agents potentiate each other (Lebowitz et al., 1980) perhaps by actions at different sites (Bowman, 1980). Similarly, the presynaptic effect of pancuronium, as indicated by train-of-four fade, increases with time (Robbins et al., 1984) and this might be encouraged by pre-curarization. In the present study, the degree of fade was no different between single and divided doses. Consequently, there is no need to involve a separate mechanism of action.

The acceleration of onset in these paediatric patients was less than that seen in adults. In part, this was a reflection of the shorter onset time in children, so that the differences in absolute terms were less. Also, although attempts were made to standardize the conditions and to remove bias by randomization of patients, some differences remained. For example, the adult patients given divided doses were statistically younger than those receiving the bolus dose (44.9 ± 2.9 *v.* 59.4 ± 2.7 yr). Moreover, with changes in the order of only 20–30% in children and with the degree of individual variation seen in the study, larger numbers are required before the null hypothesis can be rejected reliably (Glantz, 1981). For example, it can be calculated that approximately 100 infants would be required to demonstrate a statistically significant shortening of onset with divided doses (Cohen, 1977).

In conclusion, the onset of neuromuscular blockade in paediatric patients can be accelerated by administering pancuronium in divided doses. However, the difference is so small and is over-shadowed by the quicker onset in small children, that such a technique does not appear to convey any clinical advantage.

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COMPARISON OF FOUR NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN THE SUPPRESSION OF THE OCULOCARDIAC REFLEX DURING STRABISMUS SURGERY IN CHILDREN

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SUMMARY

Eighty children (aged 2–12 yr) undergoing strabismus surgery were randomly assigned to receive tubocurarine, alcuronium, pancuronium or vecuronium during anaesthesia with thiopentone, fentanyl and nitrous oxide in oxygen. Heart rate and rhythm were recorded before and after the induction of anaesthesia and before and during traction on an extraocular muscle. End-tidal carbon dioxide concentration and the degree of neuromuscular blockade were monitored. Alcuronium seemed to give more protection against the oculocardiac reflex (defined as a 20% decrease in heart rate) than did tubocurarine, pancuronium or vecuronium.

The oculocardiac reflex may occur during surgical traction on an extraocular muscle. Atropine and glycopyrrolate diminish its incidence (Bosomworth, Ziegler and Jacoby, 1958; Moonie, Rees and Elton, 1964; Alexander, 1975; Meyers and Tomeldan, 1979; Hunsley, Bush and Jones, 1982; Mirakhur et al., 1982; Karhunen, Cozanitis and Brander, 1984) and gallamine is known to give considerable protection against bradycardia during strabismus surgery in spontaneously breathing patients receiving halothane, ether or cyclopropane (Deacock and Oxer, 1962; Reed and McCaughey, 1962; Dewar, 1976). Otherwise, little attention has been paid to the selection of individual anaesthetic agents as a means of decreasing the incidence of bradycardia during surgery on the extraocular muscles.

The effects of the non-depolarizing neuromuscular blocking agents tubocurarine, alcuronium, pancuronium and vecuronium on muscarinic receptors differ (Bowman, 1982). Thus we decided to compare these four agents with respect to their ability to obtund the oculocardiac reflex in children.

PATIENTS AND METHODS

Eighty children (ASA group 1), aged between 2 yr and 12 yr, undergoing strabismus surgery were studied with the approval of the institutional ethics committee. The children were premedicated with oxycodone 0.14 mg kg^{-1} and atropine 0.01 mg kg^{-1} i.m. 30–45 min before the induction of anaesthesia. On arrival of the patient in the operating theatre, surface electrodes were attached to allow recording of leads I, II and III of the electrocardiogram (Elema Mingograph, Stockholm, Sweden). Following venous cannulation, anaesthesia was induced with fentanyl 2 μg kg^{-1} and thiopentone 6 mg kg^{-1}, and maintained with 65% nitrous oxide in oxygen administered by face mask. The ulnar nerve was stimulated supramaximally at the wrist with surface electrodes using repetitive train-of-four stimuli (2 Hz for 2 s at 20-s intervals). Evoked potentials from the adductor pollicis muscle were recorded continuously (Datex, Helsinki, Finland).

Tracheal intubation was performed after the administration of one of four non-depolarizing neuromuscular blocking agents. Four groups of 20 children received, on a random basis, tubocurarine 0.5 mg kg^{-1}, alcuronium 0.25 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} or vecuronium 0.1 mg kg^{-1}. The lungs were ventilated with a Servo-ventilator and end-tidal carbon dioxide concentration was main-

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tained in the range 5±0.5% (Datex, Helsinki, Finland).

The electrocardiogram was recorded before and after the induction of anaesthesia, and before and during traction on the extraocular muscles. Heart rate was calculated from the mean of two R–R intervals, and during traction the slowest heart rate was used for analysis. A 20% decrease in the heart rate during traction on an extraocular muscle was considered to be evidence of an oculocardiac reflex. If surgery included correction of more than one muscle, only those changes noted during the operation on the first muscle were used in the study.

If an undesirable increase in heart rate occurred, a supplementary dose of fentanyl or thiopentone or both, was administered. When the amplitude of the first twitch exceeded 30% of the reference value, an additional dose of neuromuscular blocker was given. At the end of surgery, neostigmine 0.04 mg kg^{-1}, with atropine 0.02 mg kg^{-1}, was administered to antagonize any residual neuromuscular blockade.

Statistical significance was tested with Student's *t* test, and the value $P < 0.05$ was considered to be significant.

RESULTS

Details of the patients and surgery are shown in table I. The mean interval between premedication and induction of anaesthesia was 43–44 min, and the duration of surgery 22–25 min, in all groups. Repositioning of the lateral rectus muscle was the most common operation. A supplementary dose of fentanyl or thiopentone, or both, was given to one, four, three and two children in the tubocurarine, alcuronium, pancuronium and vecuronium groups, respectively, and an additional dose of the relevant neuromuscular blocking drug to one, two, one and five children in the respective groups before traction was applied to the extraocular muscle.

At the time of traction on the extraocular muscle, the first twitch amplitude was depressed to less than 22% of the control value in each group (table II). Single twitch amplitude was less than 10% of control in 13 children in the pancuronium group. The same degree of neuromuscular blockade was seen in six, two and seven children in the tubocurarine, alcuronium and vecuronium groups, respectively. At the time of muscle traction there was no evidence of neuromuscular transmission at all in three children in the pancuronium group and in one child in each of the tubocurarine and vecuronium groups.

Heart rates in the four groups at different stages of anaesthesia and surgery are shown in table III and the changes in mean heart rate are illustrated in figure 1. After the induction of anaesthesia there was a statistically significant increase in heart rate in the alcuronium group and a statistically significant decrease in the vecuronium group. Traction on an extraocular muscle produced statistically significant decreases in mean heart rate in the tubocurarine, pancuronium and vecuronium groups. Mean heart rate returned to the awake value during muscle traction in the alcuronium group.

The oculocardiac reflex was noted in 65–75% of

TABLE I. *Details of patients and surgery (mean values ± SD) (*No. patients)*

	Tubocurarine group ($n = 20$)	Alcuronium group ($n = 20$)	Pancuronium group ($n = 20$)	Vecuronium group ($n = 20$)
Age (yr)	8.2 (2.3)	6.3 (2.5)	7.1 (3.0)	7.0 (2.5)
Weight (kg)	28.8 (10.2)	22.8 (7.1)	25.9 (10.5)	26.0 (9.2)
Height (cm)	129.2 (14.3)	118.8 (17.3)	123.0 (21.7)	124.2 (15.0)
Premedication–induction time (min)	44.2 (13.6)	42.9 (6.8)	43.7 (14.4)	42.9 (11.3)
Duration of surgery (min)	23.7 (8.3)	23.2 (7.2)	21.8 (6.9)	24.7 (7.0)
Lateral muscle surgery*	12	10	12	17
Retroposition of muscle*	18	19	16	19

TABLE II. *Incidence of the oculocardiac reflex and arrhythmias with concomitant assessment of neuromuscular blockade in the four patient groups. First values are number of patients. T1 = height of single twitch amplitude compared with pre-relaxant value of 100%; TOF = train-of-four percentages.* *$P < 0.02$ *(Chi-square test)*

	Tubocurarine group ($n = 20$)	Alcuronium group ($n = 20$)	Pancuronium group ($n = 20$)	Vecuronium group ($n = 20$)
Oculocardiac reflex	15	6*	13	14
Arrhythmias	6	—	1	5
T1	15.4 (8.5)	21.3 (14.6)	7.5 (7.7)	18.0 (16.4)
TOF	12.0 (14.7)	13.7 (13.5)	2.7 (8.2)	4.3 (7.4)

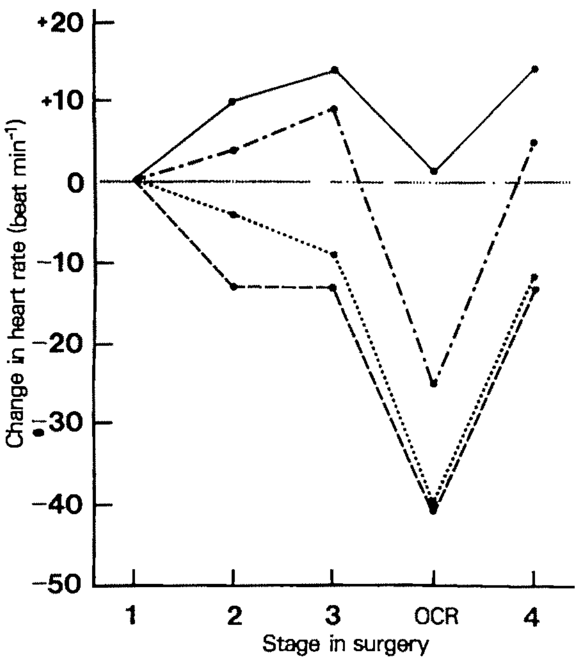

FIG. 1. Changes in mean heart rate (beat min^{-1}) during different stages in strabismus surgery: (1) heart rate before induction of anaesthesia; (2) before surgery; (3) during surgery before traction on the extraocular muscle; OCR (oculocardiac reflex) = the slowest heart rate observed during traction on the extraocular muscle; (4) heart rate after traction on the muscle. —— = Alcuronium; --- = pancuronium; ...... = tubocurarine; —— = vecuronium.

the patients in the tubocurarine, pancuronium and vecuronium groups, and in 30% of the alcuronium group (table II). Concomitant arrhythmias with absent, wandering or abnormal P waves and normal QRS complexes were seen in six, one and five patients in the tubocurarine, pancuronium and vecuronium groups, respectively. In the alcuronium group no junctional escape rhythm was seen. Two children showed occasional widening of the QRS complex: one was noted in the alcuronium group before the induction of anaesthesia and the other was in the pancuronium group and did not seem to be related to traction on the extraocular muscle.

DISCUSSION

In this study an attempt was made to produce a consistent depth of anaesthesia and degree of neuromuscular blockade at the time of traction on an extraocular muscle in order to allow comparison between the effects of different neuromuscular blocking agents. It was observed that the incidence of the oculocardiac reflex did not depend on the extraocular muscle involved, confirming the findings of Blanc and co-workers (1983) and Milot and colleagues (1983), who emphasized that gentle, gradual manipulation of the extraocular muscle is required to diminish the frequency of

TABLE III. *Mean heart rates (beat min^{-1}) (SD) of the four patient groups during different stages of the procedure. Compared with awake value:* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

	Tubocurarine group ($n = 20$)	Alcuronium group ($n = 20$)	Pancuronium group ($n = 20$)	Vecuronium group ($n = 20$)
Awake	121.1 (17.7)	121.5 (19.6)	114.6 (21.9)	117.7 (21.7)
Before surgery	116.6 (16.9)	131.0 (12.4)*	118.3 (12.6)	105.2 (14.6)**
Before traction	112.5 (13.3)	135.2 (11.4)**	123.3 (17.3)*	105.0 (13.5)**
Slowest rate	81.5 (22.9)***	122.5 (19.1)	88.7 (17.6)***	78.3 (18.2)***
After traction	109.6 (14.5)*	135.8 (12.1)**	119.9 (16.8)	105.8 (15.7)**

the reflex. In our study 56% of the operations were performed by the same ophthalmologist.

In an earlier study on adult patients during halothane anaesthesia, we found that atropine i.m. 45 min before the induction of anaesthesia diminished the frequency of the oculocardiac reflex in a dose-dependent manner (Karhunen, Cozanitis and Brander, 1984). In spite of the use of atropine, we found a decrease in heart rate during traction in all four patient groups in this study (fig. 1).

Our results show that the effects of individual non-depolarizing neuromuscular blocking agents on heart rate and the frequency of the oculocardiac reflex differed. Alcuronium caused a significant tachycardia during anaesthesia and surgery. Thus the mean heart rate in the alcuronium group decreased to the awake value during traction on an extraocular muscle, in contrast to a significant decrease in heart rate to less than the awake value in the other groups. The oculocardiac reflex and arrhythmias occurred significantly less often in the alcuronium group than in the other groups.

The different effects of tubocurarine and alcuronium on heart rate in these children can be explained by the atropine-like effect of alcuronium on the cholinergic receptors in the heart (Hughes and Chapple, 1976), as well as by the ganglion blocking activity of tubocurarine (Guyton and Reeder, 1950). Pancuronium seems to possess the same vagolytic effect on the heart as does alcuronium (Saxena and Bonta, 1970; Hughes and Chapple, 1976; Bowman, 1982), being additionally capable of facilitating noradrenaline release and blocking the re-uptake of noradrenaline at sympathetic nerve terminals (Marshall and Ojewole, 1979). The greater decrease in heart rate seen in this study with pancuronium than with alcuronium still lacks an explanation.

Vecuronium caused a significant reduction in mean heart rate (fig. 1), consistent with an earlier study by Salmenperä and colleagues (1983) during high-dose fentanyl anaesthesia. Traction on an extraocular muscle resulted in a further decrease in heart rate, and junctional escape rhythms appeared in 25% of children. As confirmation of other work (Marshall et al., 1980), no evidence for a vagolytic action of vecuronium was observed.

In conclusion, when a non-depolarizing neuromuscular blocking drug is used during strabismus surgery with nitrous oxide, fentanyl and thiopentone, alcuronium may be preferred to tubocurarine, pancuronium and vecuronium because of its favourable vagolytic effect on the heart.

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ANTAGONISM OF THE MUSCARINIC EFFECTS OF EDROPHONIUM WITH ATROPINE OR GLYCOPYRROLATE

A Comparative Study

R. K. MIRAKHUR

SUMMARY

The efficacy of atropine or glycopyrrolate in doses of 10 or 20 μg kg^{-1} and 5 or 10 μg kg^{-1}, respectively, has been compared when administered to block the muscarinic effects of edrophonium 0.5 mg kg^{-1} administered for the reversal of neuromuscular blockade. Both doses of atropine and the higher dose of glycopyrrolate prevented any edrophonium-induced decreases in heart rate; glycopyrrolate at this dose was associated with tachycardia. Atropine and edrophonium could be safely administered together in a mixture. The control of oropharyngeal secretions was adequate even with the lower doses of both anticholinergic agents. Atropine 10 μg kg^{-1} appears to be a better anticholinergic agent for use with edrophonium.

Although neostigmine is used widely to antagonize residual neuromuscular blockade edrophonium, in doses of 0.5 mg kg^{-1} or greater, has been suggested as an alternative because of its more rapid onset of action and lower incidence of muscarinic side-effects (Bevan, 1979; Kopman, 1979; Cronnelly, Morris and Miller, 1982).

Glycopyrrolate has been shown to be the anticholinergic agent of choice—in association with neostigmine—because of greater stability of heart rate and better control of secretions (Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977; Kongsrud and Sponheim, 1982). Cronnelly, Morris and Miller (1982) showed that the dose of atropine could be halved when it was mixed with edrophonium, but they did not include glycopyrrolate in their studies. Azar and his colleagues (1983) compared atropine and glycopyrrolate in a mixture with edrophonium at the doses commonly used with neostigmine, but did not assess the anticholinergic agents at lower doses.

In the present study, the efficacy of atropine at two doses in a mixture with edrophonium has been compared with that of glycopyrrolate administered similarly.

PATIENTS AND METHODS

After approval from the local ethics committee and informed patient consent, 100 adult patients (ASA grade 1) were studied. All were undergoing elective surgery requiring non-depolarizing neuromuscular blocking agents. They were premedicated with diazepam by mouth and anaesthetized with thiopentone i.v., nitrous oxide and 0.5–1.0% halothane in oxygen and fentanyl in doses of up to 3 μg kg^{-1} i.v. Atracurium or vecuronium were administered to provide neuromuscular blockade. Ventilation of the lungs was adjusted to maintain the end-tidal carbon dioxide concentration around 4.5–5.0%. Neuromuscular blockade was monitored using train-of-four (TOF) stimulation delivered from a peripheral nerve stimulator, the resultant force of thumb adduction being recorded on a neuromuscular function analyser (Myograph 2000). The detailed results of the effects of edrophonium on neuromuscular transmission are not included here and will be reported separately.

The last dose of fentanyl was administered at least 20 min before, and halothane discontinued about 10 min before, the end of surgery. The oropharynx was cleared of all secretions before administration of the test drugs.

The electrocardiogram (ECG) and arterial pressure were recorded continuously from 1 min before until 10 min after administration of the test mixture. Heart rate and arterial pressure were

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TABLE I. *Patient characteristics and heart rate (mean ± SEM) before antagonism*

	Atropine		Glycopyrrolate	
	10 μg kg^{-1}	20 μg kg^{-1}	5 μg kg^{-1}	10 μg kg^{-1}
Age (yr)	40 ± 3.3	41 ± 3.5	37 ± 3.4	39 ± 3.4
Weight (kg)	65 ± 1.8	68 ± 2.5	68 ± 2.7	69 ± 2.1
Male:Female	17:8	11:14	14:11	17:8
Heart rate before reversal (beat min^{-1})	74 ± 3.1	71 ± 2.5	70 ± 2.1	74 ± 3.2

again recorded at 20 and 30 min. Oropharyngeal secretions were assessed before extubation and graded arbitrarily as "acceptable" or "excessive". Extubation was carried out when neuromuscular blockade was antagonized adequately (TOF ratio of 0.7 or more) and spontaneous ventilation had resumed.

Edrophonium was administered, in a dose of 0.5 mg kg^{-1} in a mixture with either atropine 10 or 20 μg kg^{-1} or glycopyrrolate 5 or 10 μg kg^{-1}, as soon as surgery had finished, but not before at least one contraction in response to TOF stimulation was present. The anticholinergic components were administered in a double-blind manner. Any patient whose neuromuscular blockade was not antagonized adequately by this dose of edrophonium received further doses, but was excluded from the study. An additional dose of the same anticholinergic agent (atropine 0.5 mg or glycopyrrolate 0.25 mg) was administered if the heart rate decreased to less than 50 beat min^{-1}. Such patients were not excluded from the study.

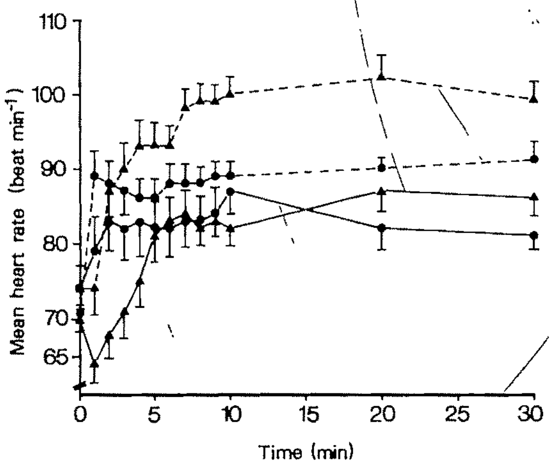

FIG. 1. Mean heart rates (± SEM) following administration of edrophonium 0.5 mg kg^{-1} in a mixture with atropine 10 μg kg^{-1} (●——●); atropine 20 μg kg^{-1} (● — ●); glycopyrrolate 5 μg kg^{-1} (▲——▲); glycopyrrolate 10 μg kg^{-1} (▲—▲).

The ECG were examined in detail for changes in heart rate and rhythm. The heart rate changes in each group were analysed by a paired *t* test. The incidence of arrhythmia and the quality of secretions was analysed using Fisher's Exact test.

RESULTS

There were 25 patients in each of the four groups. They were comparable with respect to their physical characteristics and heart rate before antagonism of the neuromuscular blockade (table I). The changes in heart rate after administration of the test mixtures are shown in figure 1. The administration of atropine produced an immediate, dose-related and significant (P from < 0.001 to < 0.05) increase in heart rate, except at 1 min after 10 μg kg^{-1}, when the increase was minimal (5 beat min^{-1}). Mean heart rate increased to a peak of 83 beat min^{-1} at 2 min following the 10-μg kg^{-1} dose and to 89 beat min^{-1} at 1 min following the 20-μg kg^{-1} dose of atropine ($P < 0.025$ and $P < 0.001$, respectively). Glycopyrrolate 5 μg kg^{-1} was associated with an initial decrease in heart rate from a mean of 70 to 64 beat min^{-1} ($P < 0.005$). Subsequently the heart rate increased, reaching a peak of 84 beat min^{-1} at 7 min, and the increases were significant from 5 min onwards (P from < 0.001 to < 0.005). The higher dose of glycopyrrolate produced a significant ($P < 0.001$) increase in heart rate from 2 min onwards, reaching a peak of 100 beat min^{-1} at 10 min.

Two patients receiving glycopyrrolate 5 μg kg^{-1} required additional anticholinergic to correct a decrease in heart rate to less than 50 beat min^{-1} occurring in both 2 min after the administration of the test drugs. The heart rates in all other patients remained above 50 beat min^{-1}, even with the lower doses of the anticholinergic drugs.

TABLE II. *Incidence (number of patients) and type of arrhythmia observed. *One patient in this group had both junctional rhythm and ventricular ectopic beats*

	Atropine		Glycopyrrolate	
	10 μg kg^{-1}	20 μg kg^{-1}	5 μg kg^{-1}	10 μg kg^{-1}
Total number showing arrhythmias	4	7*	6	4
Junctional rhythm	2	6	4	3
Ventricular ectopic beats	2	2	1	0
Prolongation of P–R interval	0	0	1	1

Arrhythmias were observed in 21 patients. The principal arrhythmia was junctional rhythm which was observed in 15 patients. The distribution amongst the various groups is given in table II. There was no difference in the overall incidence of arrhythmia amongst the groups; the arrhythmias resolved spontaneously without any treatment.

The changes in systolic arterial pressure were minimal: there were significant increases just before and following extubation.

The assessment of oropharyngeal secretions is depicted in figure 2. It is obvious that even the lowest doses of the anticholinergic drugs were associated with acceptable control of secretions in approximately 90% of patients. No significant differences were observed between the groups.

DISCUSSION

Atropine and glycopyrrolate differ in their influence on heart rate when used with edrophonium. Whereas even the lower dose of the former produces an immediate increase, the lower dose of the latter is associated with a small decrease initially. The reason for this is probably the slower time to peak effect of glycopyrrolate compared with that of atropine (Mirakhur, Jones and Dundee, 1981), and the comparatively rapid onset of the effect of edrophonium (Bevan, 1979; Cronnelly, Morris and Miller, 1982).

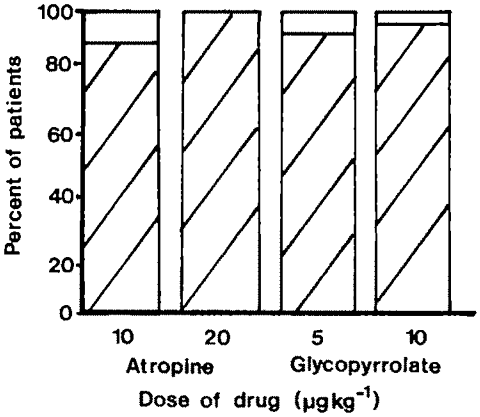

FIG. 2. Secretions following reversal. Cross-hatched columns = acceptable; open columns = excessive.

Although the initial decrease in heart rate of 6 beat min^{-1} observed following glycopyrrolate 5 μg kg^{-1} may not appear clinically important, the requirement for additional glycopyrrolate in two patients in this group as a result of a decrease in heart rate to below 50 beat min^{-1} perhaps points to the inadequacy of this dose. Azar and colleagues (1983) also demonstrated that glycopyrrolate 0.5 mg (approximately 7.7 μg kg^{-1}) was inadequate when used with edrophonium 0.5 mg kg^{-1}. On the other hand, a 10-μg kg^{-1} dose was associated with excessive tachycardia. Atropine 10 μg kg^{-1} was associated with more stable heart rates which were similar to those produced by glycopyrrolate 5 μg kg^{-1} after 4 min, but without the initial decrease in heart rate. The higher dose of atropine was also associated with unnecessarily high heart rates, but not of the same magnitude as that observed with the higher dose of glycopyrrolate. The adequacy of the lower dose of atropine with edrophonium as the anticholinergic agent was shown also by Cronnelly, Morris and Miller (1982). These authors reported that atropine, even in a dose of 7 μg kg^{-1}, was adequate with doses of edrophonium approximately the same as those used in the present study.

It has been suggested on theoretical grounds, and without any measurement of heart rate, that atropine be administered before edrophonium (Bevan, 1979; Baird, Bowman and Kerr, 1982). This, however, appears to be unnecessary, not only from the results of the present study, but also from the studies of Cronnelly, Morris and Miller (1982) and Azar and co-workers (1983). Our data would also suggest that the onset of action of atropine is perhaps similar, if not faster, than that of edrophonium, since both doses of atropine produced an immediate increase in heart rate.

The overall picture from the present study suggests that edrophonium exerts weak muscarinic effects, since even the lower dose of atropine was sufficient to prevent bradycardia. This is supported further by the acceptable control of oropharyngeal secretions achieved using the lower doses of the anticholinergic drugs.

In conclusion, the doses of anticholinergic agents can be decreased safely when used in association with edrophonium, in comparison with those required with neostigmine. Atropine in a dose of 10 μg kg^{-1} appears to be the agent of choice with edrophonium 0.5 mg kg^{-1} when given to antagonize neuromuscular blockade. Whereas glycopyrrolate 5 μg kg^{-1} does not provide complete protection against the edrophonium-induced decreases in heart rate, the higher dose is associated with excessive tachycardia.

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AN EVALUATION OF THE ACCURACY OF PHARMACOKINETIC DATA FOR THE COMPUTER ASSISTED INFUSION OF ALFENTANIL

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SUMMARY

The accuracy of using average alfentanil pharmacokinetic data in a computer assisted infusion pump (TIAC) to predict alfentanil plasma concentrations was tested in 35 patients (divided into three groups) receiving alfentanil and nitrous oxide in oxygen anaesthesia for lower and upper abdominal surgery. By frequently measuring the arterial plasma concentration, it was possible to determine the average prediction error for individual patients and for groups of patients. For the groups, there were no significant systematic over- or underpredictions of the alfentanil plasma concentrations (bias). However, there existed a moderate degree of variability (imprecision) within the groups, caused by deviations of measured and predicted plasma concentrations in the individual patients within each group. As a result, prediction errors of 22.2–32.5% can be expected with the average pharmacokinetic data used in this study to drive TIAC. It was concluded that, as a result of the moderate degree of imprecision, it is unwise to rely totally on the absolute values of alfentanil plasma concentrations predicted by a computer-regulated infusion pump such as TIAC. However, such devices can be used to attain rapidly a relatively stable plasma concentration that can be adjusted (titrated) to the requirements of an individual patient during anaesthesia.

In recent years, pharmacokinetic and pharmacodynamic research has developed new concepts which are applicable to the i.v. administration of anaesthetic drugs: for example, the rates of distribution and elimination in the body have been quantitated. Moreover, new i.v. anaesthetics with desirable pharmacokinetic profiles (for example, rapid elimination from the body) have been introduced. Numerous studies have defined the relationships between plasma concentrations and the therapeutic and adverse effects of i.v. anaesthetic drugs such that it is now possible to estimate the range of plasma concentrations that results in desirable drug effects (therapeutic window) for several anaesthetic drugs. In addition, knowledge is accumulating about factors (intensity of surgical stimulation, drug interactions) which may change the therapeutic window of a drug. Finally, the concept of a continuous infusion of the anaesthetic(s) to maintain the therapeutic plasma concentration(s) has been introduced.

Alfentanil is an example of a relevant drug. It has desirable pharmacokinetic and pharmacodynamic properties (Stanski and Hug, 1982): a short terminal elimination half-life, a rapid onset of action as a result of rapid blood : brain equilibration (Scott and Stanski, 1984), and a definable therapeutic window that varies with the intensity of surgical stimulation (Ausems and Hug, 1983). The continuous infusion of alfentanil (to supplement general anaesthesia with 66% nitrous oxide in oxygen) at a rate that is varied according to the patient's responses can produce satisfactory anaesthesia followed by a prompt recovery (Ausems, Hug and de Lange, 1983).

In order to utilize all of the above pharmacokinetic and pharmacodynamic concepts, a computer-driven infusion device has been developed

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(TIAC (Titration of Intravenous Agents by Computer) Janssen Scientific Instruments, Janssen Pharmaceutica, Belgium). The anaesthetist is required to provide the computer (Hewlett-Packard 86) with the appropriate pharmacokinetic data for the specific drug in the patient population. The computer then drives a calibrated infusion pump to administer the drug. The device can be used in either of two ways:

(1) The infusion pump is controlled by the user, who can give defined bolus doses or infusion rates, or both, to the patient. In this case, the computer continuously calculates the theoretical consequences of the dosing scheme in terms of plasma concentrations predicted by a two-compartment pharmacokinetic model and the pharmacokinetic data provided by the user of the drug. In this situation, TIAC provides only a prediction of the plasma concentration over time and the amount of drug in the peripheral compartment.

(2) The user defines a certain plasma concentration (or a certain amount of drug in the peripheral compartment) and the computer uses the pharmacokinetic model and data to calculate the amount of drug and the rate of infusion that the pump must deliver. To achieve the chosen plasma concentration, the computer uses a *BET* infusion scheme consisting of an initial bolus (*B*) for filling up the initial volume of distribution, the maintenance infusion rate required to replace drug that has been eliminated (*E*) and an exponentially declining infusion rate compensating for the transfer (*T*) of drug into the peripheral compartment (Schwilden, 1981). In this way the computer calculates (every 15 s) the amount of drug needed to achieve and maintain the chosen plasma concentration and adjusts the infusion rate accordingly. During anaesthesia the chosen plasma concentration may be changed by the user.

TABLE I. *Alfentanil pharmacokinetic data used in TIAC. Pharmacokinetic data of alfentanil determined in a group of seven female patients (ASA physical status 1 or 2) scheduled for minor gynaecological surgery (Schüttler and Stoeckel, 1982)*

$$C_{P(t)} = A.e^{-\alpha.t}+B.e^{-\beta.t}$$

$A = 0.44$ mg litre^{-1} $\alpha = 0.18$ min^{-1}
$B = 0.132$ mg litre^{-1} $\beta = 0.01$ min^{-1}
I.v. bolus dose = 5 mg
Distribution half-life = 4.3 min
Elimination half-life = 70 min
Clearance = 336.2 ml min^{-1}
Initial distribution volume = 10.2 litre
Steady state distribution volume = 33.3 litre

As a part of the evaluation of such computer-controlled devices, it is important to know the relationship between the computer predictions of drug concentrations and the concentrations that are actually produced in plasma. The purpose of this study was to examine the accuracy of using previously reported alfentanil pharmacokinetic data (table I) (Schüttler and Stoeckel, 1982) in the TIAC device to predict the plasma concentrations of alfentanil in patients having lower and upper abdominal surgical procedures.

PATIENTS AND METHODS

Three groups of patients were studied.

Lower abdominal group. Ten female patients, ASA physical status 1, aged 25–49 yr, scheduled for lower abdominal gynaecological surgery.

Upper abdominal group. Ten patients (4 female), ASA physical status 1, aged 23–54 yr, scheduled for upper abdominal surgery.

Interactive group. Fifteen female patients, ASA physical status 1, aged 20–50 yr, scheduled for gynaecological surgery (11 lower abdominal, four major vaginal surgery).

The patients in the first two groups were participating in clinical studies examining the pharmacokinetics and dynamics of alfentanil. In these groups the alfentanil was administered by a calibrated infusion pump (WTI, SP1002): bolus injections were administered via a syringe with the anaesthetist defining the bolus doses and rates of infusion. TIAC was used *retrospectively* to predict the alfentanil plasma concentrations that would be expected from the dosing scheme utilized for each patient. In the interactive group the TIAC was used *prospectively* to control the rate of the alfentanil infusion. All patients in each group consented to the procedure as approved by the Medical Ethics Committee of the University of Leiden.

In the lower and upper abdominal groups, anaesthesia was first induced with a bolus injection of alfentanil 150 μg kg^{-1} and subsequently maintained with 66% nitrous oxide in oxygen and a continuous infusion of alfentanil. During the maintenance of anaesthesia for the surgical procedure, bolus doses of alfentanil were administered and the alfentanil infusion rate was changed as indicated by the responses of the patients to surgical stimuli (Ausems, Hug and de Lange, 1983).

In the interactive group, the anaesthetist prospectively chose the desired alfentanil plasma concentration, whereupon the TIAC computed and administered the amount of alfentanil needed, based upon the alfentanil pharmacokinetic data described by Schüttler and Stoeckel (1982) (table I). Control measurements were made while the patient breathed oxygen, then anaesthesia was induced with alfentanil administered by TIAC and 66% nitrous oxide in oxygen. Ventilation was controlled as the patient's spontaneous effort was depressed. The chosen alfentanil plasma concentration for the induction of anaesthesia was 400 ng ml^{-1}. Thereafter the chosen plasma concentration of alfentanil was changed as indicated by the same clinical signs of adequate or inadequate anaesthesia used in the lower and upper abdominal groups (Ausems, Hug and de Lange, 1983). If the patient demonstrated clinical signs of inadequate anaesthesia, the alfentanil concentration was increased by 50 or 100 ng ml^{-1} from the initial value. If the patient did not respond at a given alfentanil concentration, the desired concentration was decreased by 50 or 100 ng ml^{-1}. All patients were premedicated with diazepam 10 mg orally 2 h before and atropine 0.5 mg i.m. 30 min before the induction of anaesthesia.

In all patients arterial blood samples were taken to determine the concentration of alfentanil in plasma. In the lower and upper abdominal groups samples were taken before and 2, 5 and 10 min after the alfentanil induction and every 10 min thereafter until the first sign of inadequate anaesthesia. Additional blood samples were obtained at the time of such signs and 2, 5 and 15 min after any supplementary bolus dose and then every 15 min until the next sign of inadequate anaesthesia appeared. In the interactive group, samples were obtained 5 min after a stable plasma concentration of the desired value was predicted by TIAC and every 10–20 min if this desired plasma concentration was not changed. A sample was also taken just before making any change in the desired plasma concentration.

Blood was collected in heparin-rinsed syringes, transferred to dry heparinized tubes and chilled in ice until centrifugation. Plasma was separated from blood and stored at −20 °C until assayed. Alfentanil plasma concentrations were determined by a radioimmunoassay or gas chromatography (Michiels, Hendriks and Heykants, 1983).

Data analysis

Linear regression was used to display the relationship between the measured and predicted alfentanil plasma concentrations for each patient in all groups. Although the regression analysis gives a good visual impression of the data in different groups of patients, it is not the optimal statistical approach to quantitate the accuracy of the population pharmacokinetic data used in TIAC (Sheiner and Beal, 1981). Therefore, the following was determined for each measured blood sample:

$$\text{prediction error (ng ml}^{-1}) = C_{\text{P(measured)}} - C_{\text{P(predicted)}}$$

$$\text{prediction error (\%)} = \frac{C_{\text{P(measured)}} - C_{\text{P(predicted)}}}{C_{\text{P(measured)}}} \times 100\,\%$$

where C_{P} was the concentration of alfentanil in plasma. The prediction error (%) scaled the prediction error (ng ml^{-1}) to the measured alfentanil value, since the alfentanil plasma concentrations changed within an individual patient during the course of anaesthesia and the concentrations differed between patients.

For each patient, it was possible to derive two measures that characterized the accuracy of the pharmacokinetic data used to programme TIAC, namely bias and precision (Colton, 1974). Bias is the mean prediction error and is an estimate of the systematic over- or underprediction of the alfentanil plasma concentration; it was calculated as follows:

$$\text{Bias} = \frac{\Sigma\ \text{prediction error (ng ml}^{-1}\text{ or \%)}}{\text{number of measurements per patient}}$$

The standard deviation of the bias is an estimation of the spread of the prediction error and can be used as a measure of precision. The bias and precision, calculated for each patient, do not provide direct information on the typical size of the prediction error if there are both over- (positive) and under- (negative) predictions in an individual patient. Therefore, we also calculated for each patient the mean absolute prediction error as follows:

$$\text{mean absolute prediction error} = \frac{\Sigma\,|\text{prediction error (ng ml}^{-1}\text{ or \%)}|}{\text{number of measurements per patient}}$$

In contrast to the mean prediction error, the mean absolute prediction error is not influenced by the positive or negative sign of the prediction

TABLE II. *Patient characteristics (mean ± SD). *Significantly different (P < 0.05) from all other groups*

Group	Number of patients	Age (yr)	Weight (kg)	Average alfentanil plasma concn (ng ml^{-1})
Lower abdominal	10	37±9	66±16	305±61
Upper abdominal	10	44±12	72±12	427±129*
Interactive	15	36±8	63±11	276±87

errors and gives direct information on the typical size of the prediction error in individual patients and groups of patients.

The bias, 95% confidence bounds of the bias, the precision and the mean absolute prediction error were calculated for each patient. By examining the degree of bias and 95% confidence bounds of the bias it was possible to determine if an individual patient had a statistically significant degree of bias ($P < 0.05$). The individual estimates of mean prediction error and mean absolute prediction error were then averaged to obtain the group performance. One-way analysis of variance ($P < 0.05$) was used to determine if a significant difference existed between the group means: if so, multiple two-tailed unpaired *t* tests with the Bonferroni correction ($P < 0.05$) were performed to examine individual group differences.

RESULTS

The three groups of patients were comparable in age, weight and ASA physical status (table II). In the lower abdominal and interactive groups the average alfentanil plasma concentrations required to block the patient's responses to surgical stimulation were approximately the same. The average alfentanil plasma concentration was significantly higher in the upper abdominal group (table II). This difference represented the higher alfentanil plasma concentrations needed to block patient's responses to the stimuli of upper abdominal surgery.

Figure 1 shows the predicted and measured alfentanil plasma concentrations for two patients in the interactive group. One graph is from a typical patient (left panel, maximal difference between measured and predicted plasma concentration 30–40 ng ml^{-1}) and the other is from the most extreme patient (right panel, difference between measured and predicted plasma concentration 100–200 ng ml^{-1}). In regard to the latter patient, it should be noted that the pattern of measured concentrations over time paralleled the predicted pattern, but the actual concentrations were approximately 150 ng ml^{-1} lower than predicted. These systematically smaller than predicted concentrations could reflect a pharmacokinetic difference (for example, this patient's clearance of alfentanil may have been twice that of the average data used to programme TIAC). However, this pharmacokinetic difference did not impede the anaesthetist's ability to increase or decrease the alfentanil concentration as required to maintain a satisfactory anaesthetic state.

To visualize the relationship between measured and predicted alfentanil plasma concentrations for all patients, we regressed, for each patient, the

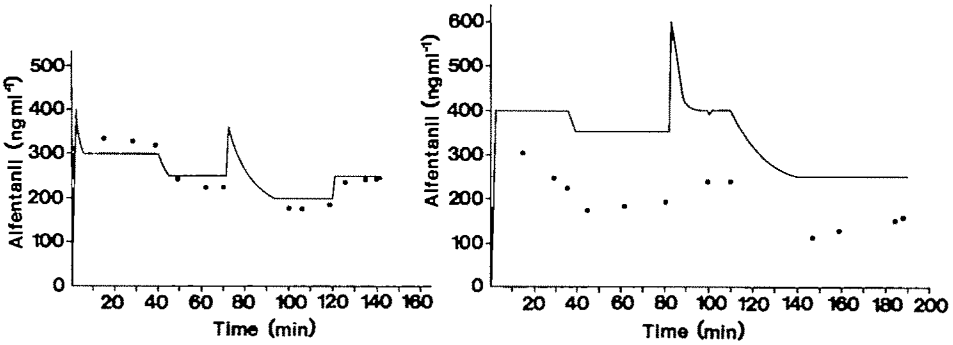

FIG. 1. Measured arterial plasma concentrations of alfentanil (·) and the predicted plasma concentrations (——) in a representative patient (left panel) and the most extreme patient (right panel); both patients from the interactive group. Note that the pattern of predicted and measured concentrations over time are similar in the right panel, but that the actual values are 100–200 ng ml^{-1} lower than predicted. See text for discussion.

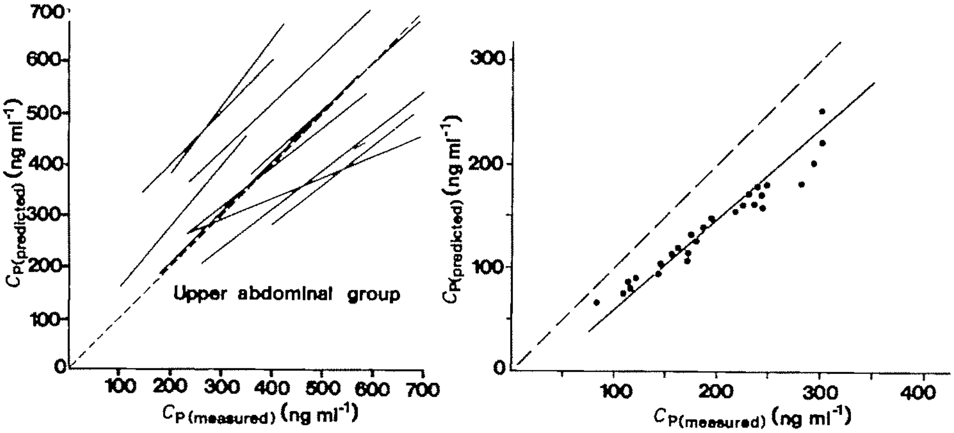

FIG. 2. Regression analysis of the predicted alfentanil plasma concentrations on the measured alfentanil plasma concentrations. Left panel: the regression lines (solid lines) for each patient of the upper abdominal group. Right panel: typical fit in one patient of the lower abdominal group (dots are data points). The interrupted line is the line of identity (measured concentration = predicted concentration).

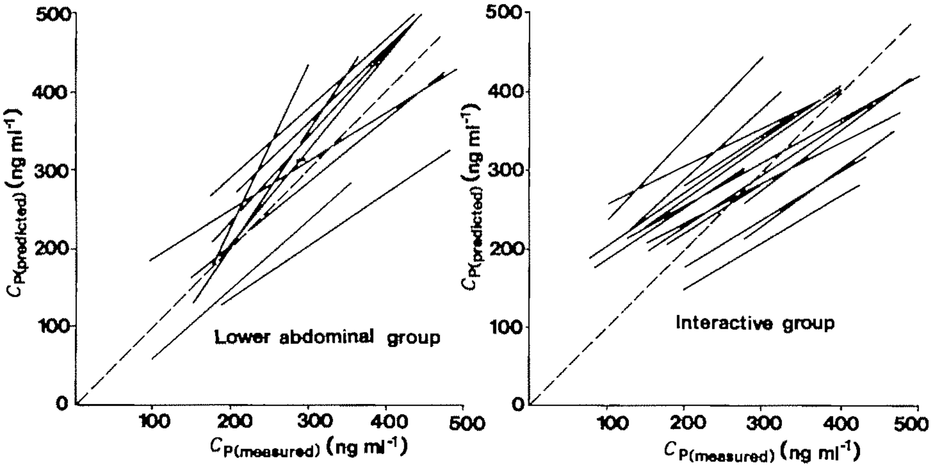

FIG. 3. Regression analysis of the predicted alfentanil plasma concentrations on the measured alfentanil plasma concentrations. Left panel: the regression lines (solid lines) for each patient of the lower abdominal group. Right panel: the regression lines for each patient of the interactive group. The interrupted line is the line of identity (measured concentration = predicted concentration).

predicted plasma concentrations on the measured plasma concentrations. Figure 2 (right panel) shows a typical fit in one patient in the lower abdominal group. In figure 3 the regression lines for each patient in the lower abdominal (left panel) and interactive group (right panel) are shown. Although individual patients deviated from the line of identity, there did not appear to be a systematic over- or underprediction of the alfentanil plasma concentrations in the overall groups. Both groups showed approximately the same degree of variability. For example a predicted value of 300 ng ml^{-1} could result in a measured value of approximately 200 or 400 ng ml^{-1} in the most extreme patients in these groups, but on an average it was 300 ng ml^{-1}. Figure 2 (left panel) shows the regression lines for the upper abdominal group. In this group the alfentanil plasma concentrations needed to suppress patient's responses during the intra-abdominal part of the operation were higher than those in the two groups which involved only lower abdominal surgery.

TABLE III. *Accuracy of the predicted alfentanil plasma concentrations in individual patients. ns = No significant bias, since the 95% confidence bounds of the bias include zero*

Group	Patient No.	*n*	Prediction error (Mean (bias) ± SD (precision)) (ng ml^{-1})	Prediction error (Mean (bias) ± SD (precision)) (%)	Absolute prediction error (Mean ± SD) (ng ml^{-1})	Absolute prediction error (Mean ± SD) (%)
Lower abdominal	1	32	−30±52	−9.8±11.68	34±49	11.9±9.52
	2	33	14±58 ns	1.3±17.57 ns	49±32	15.8±7.21
	3	28	−85±118	−27.2±23.11	87±117	28.1±22.03
	4	28	46±37	25.5±12.63	55±22	27.6±6.40
	5	34	−61±64	−20.2±19.33	67±57	22.0±17.19
	6	38	−77±46	−25.0±15.53	79±44	25.3±14.93
	7	36	−46±87	−17.8±23.21	77±60	25.3±14.29
	8	43	−32±49	−10.8±12.28	43±38	13.7±8.80
	9	27	116±52	31.6±7.05	116±52	31.6±7.05
	10	34	33±85	1.0±29.81 ns	75±50	21.0±20.85
Upper abdominal	1	31	154±43	27.1±5.45	154±43	27.1±5.45
	2	42	−216±59	−73.0±22.70	216±59	73.0±22.70
	3	25	22±40	3.3±9.37 ns	39±23	8.4±4.94
	4	34	−202±53	−72.4±28.31	202±53	72.4±28.31
	5	25	−89±62	−40.1±23.84	92±57	40.9±22.32
	6	24	123±67	21.1±8.59	123±67	21.1±8.59
	7	34	0±71 ns	−0.6±13.92 ns	51±48	9.9±9.62
	8	34	−9±36 ns	−3.7±13.13 ns	31±20	10.8±8.13
	9	30	−119±81	−33.1±21.42	126±68	34.5±18.96
	10	33	147±107	23.7±17.86	155±96	26.7±12.89
Interactive	1	10	76±56	19.8±5.04	76±56	19.8±5.04
	2	14	41±25	22.0±8.67	41±25	22.0±8.67
	3	23	68±118	10.0±20.51	83±108	18.3±13.26
	4	10	108±44	24.2±4.84	108±44	24.2±4.84
	5	11	−6±52 ns	−9.1±24.11 ns	41±31	17.2±18.58
	6	17	1±38 ns	−3.3±14.33 ns	32±19	12.2±7.64
	7	14	−63±33	−47.4±29.14	67±23	48.9±26.27
	8	25	−90±31	−50.4±24.76	90±31	50.4±24.76
	9	13	−59±23	−23.8±13.88	59±23	23.8±13.88
	10	11	−97±57	−61.9±50.55	107±32	64.7±46.44
	11	12	−75±29	−57.3±49.52	75±29	57.3±49.52
	12	12	−5±23 ns	−4.3±9.28 ns	20±10	8.8±4.69
	13	13	−38±32	−16.8±18.23	42±27	17.9±17.06
	14	12	−142±31	−78.3±26.19	142±31	78.3±26.19
	15	13	67±42	16.2±9.17	71±33	17.8±5.04

Again, there appeared to be no systematic over- or underprediction. However, there were larger individual deviations from the line of identity. For example, a predicted concentration of 400 ng ml^{-1} could result in a measured concentration of 200–600 ng ml^{-1} in the most extreme patients of the upper abdominal group (fig. 2, left panel).

Table III shows the degree of bias in the *individual* patients. All patients had some degree of bias. In only six of the 35 patients was this bias not significant (that is, the 95% confidence bounds included zero). The bias estimates showed that there were patients with systematic overprediction as well as patients with systematic underprediction of the alfentanil plasma concentration within each group.

Table IV shows the degree of bias in the three *groups* of patients. In all groups there was a slight tendency to overpredict the alfentanil plasma concentrations by 12–19 ng ml^{-1} or 5–18%. However, the bias in these groups was not significant, since the 95% confidence bounds included zero. Also, there was no significant difference in the estimates of bias between the three groups.

In addition, we calculated the mean absolute prediction error (in ng ml^{-1}, and as a percentage of the measured alfentanil plasma concentration)

TABLE IV. *Accuracy of the predicted alfentanil plasma concentrations in groups of patients. ns = No significant bias since the 95% confidence bounds of the bias include zero. There were no significant differences between groups (one way analysis of variance)*

Group	*n*	Prediction error (Mean (bias) ± SD (precision)) (ng ml^{-1})	Prediction error (Mean (bias) ± SD (precision)) (%)	Absolute prediction error (Mean ± SD) (ng ml^{-1})	Absolute prediction error (Mean ± SD) (%)
Lower abdominal	10	−12 ± 63 ns	−5.1 ± 20.27 ns	69 ± 24	22.2 ± 6.60
Upper abdominal	10	−19 ± 136 ns	−14.7 ± 37.83 ns	119 ± 65	32.5 ± 23.70
Interactive	15	−14 ± 74 ns	−17.6 ± 33.81 ns	70 ± 33	32.1 ± 21.70

which gave an estimate of the magnitude of the difference between predicted and measured plasma concentrations. Table III shows the mean absolute prediction errors for each patient. Notice that the absolute values of the mean prediction error and the mean absolute prediction error were the same in patients that consistently had only overpredictions or only underpredictions during the course of anaesthesia. In those patients (and groups of patients) that had overpredictions as well as underpredictions during anaesthesia, the mean absolute prediction error gave a more direct estimate of the typical size of the prediction error than did the mean prediction error ± SD. Table IV shows the mean absolute prediction error in the three groups. When calculated in ng ml^{-1}, the mean absolute prediction error was approximately the same in the interactive and lower abdominal group (±70 ng ml^{-1}). In the upper abdominal group it was greater (±120 ng ml^{-1}), but the differences between it and the interactive and lower abdominal groups were not significant. There was, also, no significant difference between the groups, when the mean absolute prediction error was calculated as a percentage of the measured alfentanil plasma concentration.

DISCUSSION

With inhalation anaesthetic agents it is possible to deliver a precise inspired concentration of drug, which rapidly equilibrates with the alveolar gases and reaches the blood stream for delivery to the brain: one continuously infuses the inhalation anaesthetic to the body via the lungs, resulting in relatively stable brain concentrations which can be changed in a controlled manner by changing the inspired concentration. With i.v. anaesthetic agents, it is not possible to obtain the same degree of control. With intermittent i.v. injections, the blood and brain concentrations frequently overshoot the therapeutic requirement initially, then decay to subtherapeutic concentrations in a variable period of time. These fluctuations in blood and brain concentrations can be obviated by infusing the i.v. drug continuously.

Two problems arise when using an infusion technique to administer an i.v. anaesthetic. First, it is desirable to achieve a stable blood concentration rapidly (with a constant rate infusion it takes more than four elimination half-times of the drug to approach a steady state). Second, it is desirable to be able to change from one stable blood concentration to another in a rapid and controlled manner. The changing of the desired drug concentrations according to the patient's individual needs (for example, for different intensities of surgical stimulation) will prevent the unnecessary accumulation of the i.v. anaesthetic that results from using a single stable concentration which is sufficiently high to block all of the patient's responses to the most intense surgical stimuli. With accumulation comes prolonged recovery from the effects of the drug.

Wagner (1974) has described the popular approach of a rapid then slower infusion to attain steady-state blood concentrations. This concept does result in some degree of overshoot of the desired blood concentration and does not immediately achieve the steady state concentration. Kruger-Theimer (1968) proposed the administration of a bolus loading dose followed by an exponentially declining infusion to increase rapidly and maintain the blood concentrations of a drug with multicompartment behaviour. Schwilden (1981) favoured the approach of Kruger-Theimer and developed the equations for an open, two-compartment pharmacokinetic model that are necessary to increase rapidly and then maintain constant blood concentrations. These equations have been implemented in the computer-driven infusion device, TIAC, that was evaluated in this study. A device like TIAC makes it possible to administer the exponentially-declining infusion rate necessary to achieve a certain stable plasma concentration rapidly, and can also do the continuous calculations needed to change the chosen plasma concentration as quickly as possible. Schwilden and colleagues have used the TIAC to deliver etomidate and alfentanil for short surgical procedures (Schüttler, Schwilden and Stoeckel, 1983). In their study, they achieved a mean measured etomidate plasma concentration of 0.29 μg ml^{-1} with a desired predicted value of 0.3 μg ml^{-1} and a mean measured alfentanil plasma concentration of 0.45 μg ml^{-1} with the predicted value at 0.40 μg ml^{-1}.

Before the evaluation of the clinical utility of a computer-driven infusion device such as TIAC, we evaluated its accuracy in predicting and in producing alfentanil plasma concentrations in a general surgical patient population. Our study involved the calibration of pharmacokinetic data and a pharmacokinetic model that governed a computer-driven infusion pump administering drug to a biological system—the surgical patient. The visual distillations of our study are given in figures 2 and 3. The regression lines for the three groups of patients are distributed evenly around the line of identity. The number of patients having their alfentanil plasma concentrations overpredicted was equal to the number with underpredictions. The slopes of the regression lines are close to a value of 1. A moderate degree of variability is also obvious in these figures. The statistical quantitation of the data is presented in tables III and IV. A statistically significant bias was present in most patients in the three groups (table III). However, when the individual estimates of bias in each group were pooled (table IV), there was no statistically significant bias in the three groups of patients. The mean prediction error was remarkably small: -12 to -19 ng ml^{-1} or -5.1% to -17.6%.

Evaluating the statistical estimates of precision is more difficult. In table III one sees that the degree of precision (standard deviation of the prediction error) was extremely variable between patients. In table IV the degree of precision for each group is much larger than the mean degree of bias in that group, reflecting moderate variability in the patient population. The absolute prediction error values in table IV indicate that, in the best case (lower abdominal), the mean absolute prediction error was 68.6 ng ml^{-1}, whereas in the worst case (upper abdominal) the mean absolute prediction error was 119.3 ng ml^{-1}. Expressing these values as percentages eliminates the fact that the alfentanil plasma concentrations were higher in the upper abdominal group than in the other two groups. The absolute prediction error ranged from 22.2% to 32.5%.

In the three groups of patients studied, the alfentanil pharmacokinetic data generated by Schüttler and Stoeckel (1982) (table I) did not result in a systematic over- or underprediction of alfentanil plasma concentrations; that is, there was no bias. Systematic over- or underprediction would be evidence that the pharmacokinetic data were not representative of the patient population. Schüttler and Stoeckel generated their alfentanil pharmacokinetic data from a small ($n = 7$) group of healthy female patients undergoing a short surgical procedure. Their pharmacokinetic data appear to be applicable to our patients, who were more varied in age and weight and had longer surgical procedures. Many factors might explain the moderate degree of variability found between the measured and predicted alfentanil plasma concentrations. Factors such as age, weight, gender, smoking, concurrent medication, or disease could cause variability in alfentanil pharmacokinetics. The pharmacokinetic data used in the current study did not adjust for any of these factors. Systematic pharmacokinetic research will be needed to determine if these factors are significant and if adjusting for them decreases the variability between individuals. The degree of variability found in our study was comparable to that found by other investigators reporting on large population studies of the pharmacokinetics of other drugs (Sheiner, Rosenberg and Marathe, 1977). When the technology of measuring alfentanil plasma concentrations during anaesthesia becomes available, it will then be possible to adjust the pharmacokinetic data used in an infusion device like TIAC to each individual patient during anaesthesia, thereby minimizing the influence of the between-patient variability in pharmacokinetics on the accuracy of the predicted plasma concentrations.

Does the moderate degree of between-patient variability limit the clinical utility of a device like TIAC? It is unwise to rely totally on any device as a means of predicting alfentanil plasma concentrations from rates of administration defined by the anaesthetist. Individual patients may deviate from the average pharmacokinetic behaviour, and there is the potential for substantial errors. A TIAC-like device can, however, be used to obtain relatively stable alfentanil plasma concentrations rapidly and then adjust these concentrations in a regular and controlled manner depending upon the clinical responses. If the clinical signs indicate inadequate anaesthesia, it is obvious that the alfentanil plasma concentrations need to be increased. A computer-regulated infusion device like TIAC allows one to make these incremental steps in a defined manner. Less obvious, but equally important, is the decreasing of the alfentanil plasma concentrations if there are no signs of inadequate anaesthesia. The latter is necessary in order to approach the minimal plasma concentration needed to block the individual patient's responses to surgical stimuli and, thereby, prevent any unnecessary accumulation of alfentanil—which will prolong the recovery time. Devices such as TIAC allow this titration of i.v. anaesthetic administration in a way that is analogous to the current use of a precision vaporizer for an inhalation anaesthetic.

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OUTPATIENT TERMINATION OF PREGNANCY: HALOTHANE OR ALFENTANIL-SUPPLEMENTED ANAESTHESIA

K. M. COLLINS, O. M. PLANTEVIN, R. H. WHITBURN AND J. P. DOYLE

SUMMARY

Inhalation anaesthesia with halothane was compared with i.v. alfentanil in 66 unpremedicated patients undergoing suction termination of pregnancy as outpatients. Blood loss was significantly greater in the halothane group with a mean loss of 213 ml, compared with a mean loss of 89.8 ml in the alfentanil group. There was a greater frequency of nausea and vomiting in the alfentanil group, but no reduction in abdominal pain or need for analgesia after operation. Positive relationships were found between blood loss and duration of anaesthesia and between blood loss and gestational age in the halothane group, but not in the alfentanil group. We conclude that alfentanil-supplemented anaesthesia is satisfactory for suction termination of pregnancy when rapid recovery is required or the duration of the procedure is likely to be long, but that halothane anaesthesia cannot be recommended, especially if the procedure is long.

Vaginal termination of pregnancy is one of the most common gynaecological operations. In 1982, this procedure was performed in approximately 130000 patients in England and Wales, 36828 being day-patients (Statistics, 1982). Since day-stay surgery is preferred by the majority of patients and makes efficient use of manpower and facilities, the percentage of operations performed on this basis is likely to increase.

Although aspiration termination of pregnancy up to 12 weeks is a safe procedure (Grimes and Cates, 1979), uterine haemorrhage remains a potential hazard. Loung, Buckle and Anderson (1971) found that, in a series of 1000 patients, 309 lost more than 200 ml of blood. Many factors contribute to this: the oxytocic agent (Garrioch, Gilbert and Plantevin, 1981), gestational age (Lane Report, 1974), anaesthetic technique (Cullen, Margolis and Eger, 1970; Dunn et al., 1973; Hackett et al., 1982) and duration of anaesthesia (Hackett et al., 1982). Local anaesthesia has been associated consistently with a smaller blood loss than general anaesthesia, and inhalation agents with a greater loss than i.v. techniques. However, many of the earlier studies depended on insensitive measurement techniques and most were carried out in inpatients whose premedication may have influenced the outcome. Grant (1980) stated that there was no clear evidence to suggest that one general anaesthetic technique was more or less likely to induce serious haemorrhage. Hackett and others (1982) found that, in unpremedicated day patients undergoing suction termination of pregnancy, the blood loss was significantly greater during enflurane anaesthesia than when fentanyl was used, but the mean blood loss was only 73 ml, compared with 43.9 ml in the fentanyl group, which also had the highest individual loss. They concluded that either technique was satisfactory.

Inhalation anaesthesia is preferred by the majority of anaesthetists in the U.K. and halothane is the inhalation agent most commonly used. It is considerably less expensive than either enflurane or isoflurane, but its use for termination of pregnancy is controversial although there are no data available, based on use of an accurate

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measurement technique, concerning blood loss in such procedures.

Alfentanil is a new potent opioid analgesic which has a very rapid onset of action and the shortest duration of effect of an opioid (Niemegeers and Janssen, 1981), making it particularly well suited for outpatient anaesthesia.

This study was undertaken to assess the blood loss and anaesthetic morbidity in unpremedicated day patients undergoing suction termination of pregnancy with either halothane or alfentanil-supplemented anaesthesia.

PATIENTS AND METHODS

Clinical procedures

Sixty-six patients admitted for day-stay suction termination of pregnancy of less than 12 weeks gestation were studied and randomly allocated to one of two groups. All patients were in ASA group 1 or 2. No premedication was given. In the halothane group, anaesthesia was induced with methohexitone 2 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen and 1.5% halothane until cervical dilatation was complete, when halothane was discontinued. The alfentanil group received alfentanil 7 μg kg^{-1} followed by methohexitone. Anaesthesia was maintained with 70% nitrous oxide in oxygen and incremental doses of alfentanil 0.1–0.2 mg given regularly at 2–4 min intervals depending on the patient's initial response to the drug, the progress of surgery and the respiratory rate. Care was taken not to discontinue nitrous oxide until the procedure was completed and the patient ready to be moved from the operating table. Oxytocin 5 units was administered i.v. to all patients at the onset of cervical dilatation.

Blood loss was measured using the method described by Garrioch, Gilbert and Plantevin (1981). A polythene bag was attached around the introitus on completion of the perineal draping, so that all uterine loss other than that removed by aspiration was collected. Karmen curettes and aspiration tubing were washed free of products. The products of termination and blood-stained swabs were made up to 750 ml with water, and mixed with an equal volume of 10% sodium hydroxide. The alkaline haematin method of Hallberg and Nielsson (1964) was used to determine blood volume. Precision experiments showed results to vary less than 3%, and solutions stored at room temperature and in darkness had a half-life of 12 weeks. In practice, measurements were made within 72 h.

Duration of anaesthesia and the frequency of anaesthetic complications such as coughing, salivation, hiccup, laryngeal stridor, apnoea or limb movements were noted. In the recovery room, observations were made by the nursing staff, who did not know to which group patients had been allocated. Recovery of consciousness was assessed as the time at which the patient first opened her eyes in response to her name. The frequency of nausea, vomiting, abdominal pain and the need for medication after the operation were noted by the recovery room staff during the first 1 h and subsequently until discharge.

Statistical analysis

Initially, as in our previous study (Hackett et al., 1982), we had chosen to use the group sequential design based on nausea and vomiting, the anaesthetic agent being considered a "failure" for a particular patient if she had either moderate or severe nausea with or without vomiting. The analysis was carried out on groups of 20 patients. However, the trial was stopped after 66 patients had been studied before significance was reached, when it became obvious that blood loss was unacceptably high.

The Chi-square test with Yates' correction where appropriate and Student's t test were used to evaluate the significance of differences between the two groups. Values were considered significant if $P < 0.05$. Regression analyses were performed of blood loss in relation to anaesthetic agent, gestational age and duration of anaesthesia.

RESULTS

There were no statistically significant differences between the two groups with respect to age (halothane group: range 16–38 yr, mean 24.3 yr; alfentanil group: 16–36 yr, mean 24 yr), weight (halothane group: mean 58.7 kg; alfentanil group: 58.6 kg), medical status, previous anaesthesia and previous anaesthetic problems. Table I shows the data for gestational age, duration of anaesthesia, recovery time and anaesthetic complications. Complications were classified as minor if they did not interfere with anaesthesia or surgery and as severe if the procedure was delayed or difficult. Apnoea was defined as no spontaneous respirations for more than 30 s.

TABLE I. *Gestational age, duration of anaesthesia, recovery time and anaesthetic complications in the two groups of patients. (ns = Not significant)*

	Halothane ($n = 33$)	Alfentanil ($n = 33$)	χ^2	P
Gestation (weeks)				
5–6	3	1		
7–8	5	9		
9–10	21	14	5.46	ns
11+	4	9		
Anaesthetic time (min)				
Range	8–19	6–17		
Mean	11.42	11.18		ns
SEM	0.41	0.46		
Recovery time (min)				
Range	2–25	1–8		
Mean	10.78	3.18	7.89	$P < 0.001$
SEM	0.88	0.39		
Anaesthetic complications				
Hiccup	7 (21%)	4 (12%)		ns
Salivation	3 (9%)	2 (6%)		ns
Cough	10 (30%)	1 (3%)	8.97	$P < 0.05$
Laryngeal stridor	3 (9%)	1 (3%)		ns
Apnoea	0	1 (3%)		ns
Limb movement	1 (3%)	9 (27%)	5.77	$P < 0.05$

Anaesthetic morbidity

The duration of anaesthesia was similar in both groups and there was no statistically significant difference in the overall frequency of complications (18 patients in the halothane group and 12 patients in the alfentanil group). However, coughing was 10 times more frequent in the halothane group, and in two cases was considered severe. Limb movement was nine times more frequent in the alfentanil group, although in no patient did it delay surgery. Apnoea occurred in one patient in the alfentanil group following induction of anaesthesia and again after the first increment; it was of short duration and did not require assisted ventilation. Increments of alfentanil were given to all patients (mean 0.4 mg).

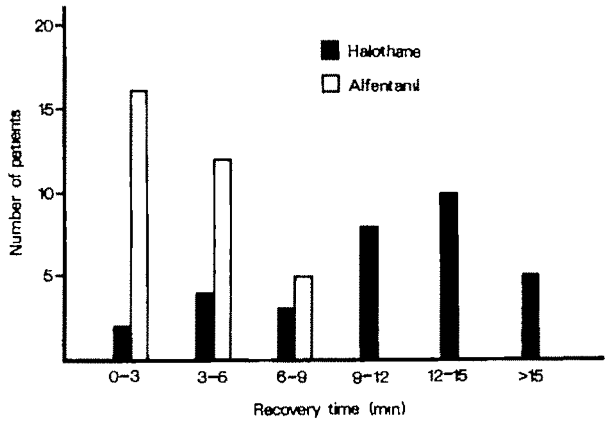

FIG. 1. Recovery times in two groups of patients.

Operating conditions

Cervical dilatation was difficult in three patients: two in the alfentanil group and one in the halothane group. Aspiration was considered easy in all patients and no differences between the two groups were reported.

Recovery time

The mean recovery time was 10.78 min (range 2–25 min) in the halothane group and 3.18 min (range 1–8 min) in the alfentanil group, a difference which was statistically significant ($P < 0.001$). More than 80% of patients in the alfentanil group were awake in the first 6 min, while at that time fewer than 20% of patients in the halothane group were awake (fig. 1). No patient had any recall of the procedure.

Blood loss

Blood losses are shown for each patient in figure 2, together with the mean loss (horizontal bar). Both the range and the mean loss were greater in the halothane group (range 28–725 ml, mean

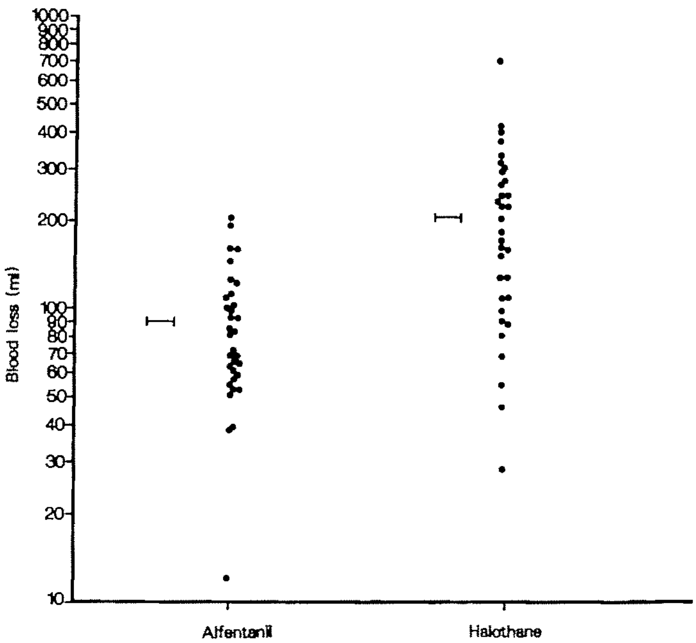

FIG. 2. Blood losses for each patient at vaginal termination of pregnancy in the two treatment groups, and mean loss.

TABLE II. *Details of the three patients in the halothane group in whom blood losses exceeded 400 ml*

	Gestational age (weeks)	Duration of anaesthesia (min)	Blood loss (ml)
Patient 18	9–10	10	403
Patient 22	9–10	16	429
Patient 65	11+	17	723

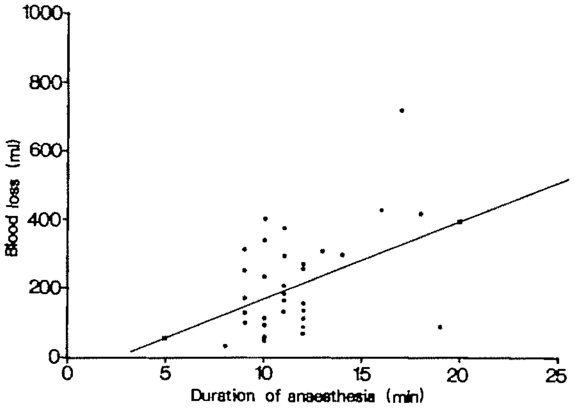

FIG. 3. Relationship between blood loss and duration of anaesthesia in patients receiving halothane.

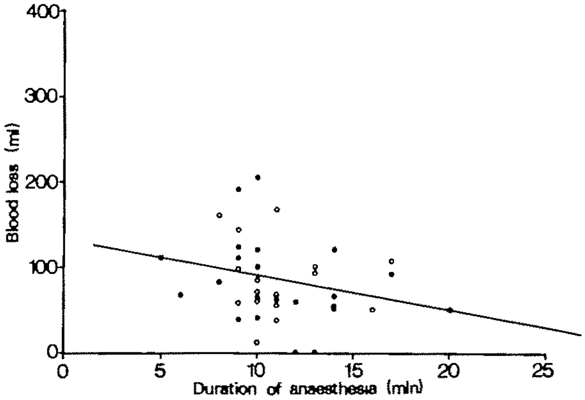

FIG. 4. Relationship between blood loss and duration of anaesthesia in patients receiving alfentanil-supplemented anaesthesia.

213 ml) than in the alfentanil group (range 12–207 ml, mean 89.8 ml) ($P < 0.001$). Excluding three patients who had blood losses greater than 400 ml, the mean loss was 199.4 ml. Table II gives details of those three patients.

Figure 3 shows that blood loss increased with duration of anaesthesia in the halothane group ($r = 0.405$; $P < 0.05$), but a negative, rather than positive, relationship was found between blood

TABLE III. *Frequency of abdominal pain and analgesic requirement in two groups of patients. (ns = Not significant (P < 0.05))*

	Halothane ($n = 33$)	Alfentanil ($n = 33$)	P
Abdominal pain			
Nil	6 (18%)	7 (21%)	ns
Slight	15 (46%)	17 (52%)	ns
Moderate/severe	12 (36%)	9 (27%)	ns
Analgesic given	16 (48%)	14 (42%)	ns

loss and duration of anaesthesia in the alfentanil group (fig. 4).

There was a significant relationship between blood loss and gestational age in the halothane group ($r = 0.374$, $P < 0.05$), but not in the alfentanil group.

Nausea and vomiting

Ten patients in the alfentanil group and three patients in the halothane group complained of moderate or severe nausea and vomiting. This difference was statistically significant ($P < 0.05$). A further 13 patients in the alfentanil group and two patients in the halothane group complained of mild nausea. No patient vomited after 1 h, and all symptoms of emesis had subsided by the end of 2 h. Two patients in the halothane group and seven patients in the alfentanil group (ns) received metoclopramide.

Abdominal pain

Abdominal pain was recorded as slight, moderate or severe. The frequency was similar in both groups and there was no difference in the requirement for analgesia after operation (table III).

DISCUSSION

This study was undertaken to evaluate the use of halothane and alfentanil-supplemented anaesthesia for outpatient termination of pregnancy in unpremedicated patients.

Halothane was introduced to clinical anaesthesia in 1956; its merits and disadvantages are well documented and it remains the inhalation agent most commonly used in the U.K. Like all such agents, it causes myometrial depression, but in *in vivo* studies of isolated human gravid uterine muscle (Paull and Ziccone, 1980) there was no significant difference between the degrees of uterine depression caused by halothane, methoxyflurane or enflurane in equipotent concentrations. Marx and her colleagues (1978) found no difference between post-partum intra-uterine pressures after halothane or enflurane. The depressant effect appeared to be related to the concentration of the agent and the duration of the procedure, and normal activity returned promptly on lightening of anaesthesia.

Although direct comparison is not possible between results obtained in different studies, it was surprising, in the present study, to find blood losses three times greater (mean 213 ml) during halothane anaesthesia than those (73 ml) found during enflurane anaesthesia using equipotent concentrations under similar conditions in the same outpatient theatre unit (Hackett et al., 1982), but with a different gynaecologist. This last is probably an important factor for, in addition, the mean blood loss in the alfentanil group (89.8 ml) was twice that (43.9 ml) found in the fentanyl group in the earlier study even though, in contrast to that fentanyl group, there was no positive relationship between blood loss and duration of anaesthesia in our alfentanil group. Enflurane has a lower blood/gas partition coefficient than halothane and, in clinical practice, induction and recovery are significantly faster with enflurane than with halothane anaesthesia (Govaerts and Sanders, 1975; Stanford, Plantevin and Gilbert, 1979). This faster elimination may explain the smaller blood losses associated with enflurane and may be increasingly important the longer the duration of the procedure, especially the time from induction to cervical dilatation. In this study there was a positive relationship between blood loss and duration of anaesthesia and between blood loss and gestational age in the halothane group, but no relationship between gestational age and duration of anaesthesia, although this may be attributable to the small number of patients studied.

Alfentanil has a very short and intense action which, unless appreciated, may lead to difficulties and unsatisfactory conditions. In this study, good operating conditions were achieved in all patients and apnoea occurred in only one patient, was of short duration, and did not require assisted ventilation. Recovery time was remarkably short (mean 3.18 min) and all patients were awake within 8 min of the discontinuation of nitrous oxide. There were no instances of awareness, probably because nitrous oxide was not discontinued until the end of the procedure when the patient was ready to be moved to the recovery trolley. Rapid recovery is a real advantage in a busy day-stay unit as it ensures the patient's protective reflexes are present as soon as possible, relieving some of the pressure on the recovery staff, even if the discharge time is unchanged. Alfentanil has no known effect on the myometrium and is therefore unlikely to contribute to bleeding during termination of pregnancy and, in contrast to halothane, its use was not associated with a positive relationship between blood loss and duration of anaesthesia or gestational age. This is a definite advantage when the duration of the procedure is long.

Nausea and vomiting are common problems with termination of pregnancy and when potent opioids are given i.v. In this study in unpremedicated patients receiving alfentanil, the frequency of nausea (69%) was higher than we had found previously (Collins and Plantevin, 1985) or that found by Patrick and her colleagues (Patrick et al., 1984), but the low frequency of nausea associated with halothane anaesthesia was confirmed. We have found a low incidence of nausea in premedicated patients having alfentanil-supplemented anaesthesia for similar procedures and wonder if this is the result of the slower return of consciousness when plasma concentrations of alfentanil may have passed a peak. The use of incremental doses of methohexitone, by reducing the frequency of requirement for alfentanil supplements, would also reduce the incidence of nausea.

We suggest that, although both the i.v. and inhalation techniques provided satisfactory anaesthesia for suction termination of pregnancy, carried out on a day-stay basis, the effects of halothane on the myometrium are disadvantageous and its use is not, therefore, recommended.

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EFFECTS OF ALFENTANIL ON CEREBRAL VASCULAR REACTIVITY IN DOGS

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Alfentanil is a short acting analogue of fentanyl which is one-third as potent and has a higher therapeutic ratio than the parent compound as a result of its rapid elimination from plasma (Bovill et al., 1982). Alfentanil provides haemodynamic stability during anaesthesia in patients with cardiac disease when used either as an induction agent or during total i.v. anaesthesia, or both (Sebel, Bovill and Van Der Haven, 1982). Even after large doses of alfentanil, the time to awakening is short (DeLange, Stanley and Boscoe, 1981), and this short duration of action has led to its use as an infusion during prolonged anaesthesia (Bower and Hull, 1982).

The shorter duration of action of alfentanil makes it an attractive alternative to fentanyl, as a supplement to anaesthetic gases, in patients undergoing neurological procedures. Moreover, its more rapid termination of action compared with fentanyl makes retention of carbon dioxide after operation less likely (Stanski and Hug, 1982), would minimize postoperative narcotic-induced somnolence, and would allow more prompt evaluation of neurological function following surgery.

This study was undertaken to determine the effects of high doses of alfentanil (0.32 mg kg^{-1} i.v.) on cerebral blood flow and metabolism ($CMRo_2$) in the dog. In addition, the reactivity of the cerebral vasculature to hypercapnia and hypoxia, and to changes in mean arterial pressure, was determined.

SUMMARY

The effects of high dose alfentanil on the cerebral vascular responses to alterations in mean arterial pressure (MAP), arterial oxygen tension (Pa_{O_2}) *and arterial carbon dioxide tension* (Pa_{CO_2}) *were studied in 17 dogs, using the cerebral venous outflow technique. In six animals anaesthetized with sodium pentobarbitone* 30 mg kg^{-1} *i.v., bolus injection of alfentanil* 0.32 mg kg^{-1} *i.v. decreased MAP without a change in cerebral blood flow (CBF). In another group of animals* ($n = 5$) *anaesthetized with pentobarbitone* 30 mg kg^{-1} *i.v. the CBF responses to changes in MAP,* Pa_{O_2}, *and* Pa_{CO_2} *were studied. In a third group of animals* ($n = 6$) *anaesthetized with alfentanil* 0.32 mg kg^{-1} *i.v. plus pentobarbitone* $1\text{–}2 \text{ mg kg}^{-1}$ *i.v. and an infusion of alfentanil* $0.32 \text{ mg kg}^{-1} \text{ h}^{-1}$, *the CBF response to alterations in MAP,* Pa_{O_2}, *and* Pa_{CO_2} *were studied and compared with the barbiturate-anaesthetized animals. The CBF responses to hypercapnia and hypoxia in the alfentanil-anaesthetized animals were not different from those observed in animals anaesthetized with barbiturate only. The lower and upper limits of cerebral autoregulation in alfentanil-anaesthetized animals were not different from those observed in animals anaesthetized with barbiturate only. The data suggest that alfentanil, in doses sufficient to cause profound analgesia and anaesthesia, does not alter cerebral reactivity to changes in* Pa_{O_2}, Pa_{CO_2} *and MAP.*

MATERIALS AND METHODS

Animals and anaesthesia

Seventeen mongrel dogs (20–25 kg) of either sex were utilized in this study. Two basal anaesthetic

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techniques were used. Eleven animals (group 1, $n = 6$; group 2, $n = 5$) were anaesthetized initially with pentobarbitone 30 mg kg^{-1} i.v. bolus and supplemented with i.v. increments of 30 mg in response to pedal and ocular reflexes. Six animals (group 3, $n = 6$) were anaesthetized with alfentanil 0.32 mg kg^{-1} i.v. plus pentobarbitone 1–2 mg kg^{-1} and an infusion of alfentanil 0.32 mg kg^{-1} h^{-1} was administered continuously throughout the investigation. Additional increments of alfentanil 1 mg were given if movement or cardiovascular response to stimulation occurred during the surgical preparation. Pancuronium 3–4 mg i.v. was administered in all groups to minimize muscle contractions related to the electrocautery. Heparin 500 u kg^{-1} i.v. was used in all groups as the anticoagulant.

After the induction of anaesthesia, the trachea was intubated and the lungs ventilated utilizing a positive pressure respirator (Harvard Respiration Pump 607). Tidal volume and respiratory rate were adjusted to give an alveolar (end-expiratory) carbon dioxide concentration of 4% as monitored by a carbon dioxide analyser (Beckman LB2). The analyser was calibrated regularly with mixtures of carbon dioxide in air analysed to a precision of 0.1%. One femoral artery was cannulated to permit the continuous monitoring of arterial pressure. The contralateral femoral artery was cannulated and utilized for the removal of blood during those parts of the study which dealt with alterations in arterial pressure. One femoral vein was cannulated and was utilized to return the cerebral venous outflow, while the other femoral vein was cannulated and used for infusion of fluids and drugs. Rectal temperature was maintained at 38 ± 1 °C using heating lamps. All pressures were measured with Statham P-23 transducers, and all data were recorded in a Gould–Brush recorder.

Measurement of cerebral blood flow

The technique used to measure cerebral venous outflow has been described previously (Rapela and Green, 1964). The confluence of the cerebral sinuses was cannulated, and the lateral sinuses and occipital emissary veins were occluded with bone wax to eliminate communication between intracranial and extracranial venous circulations. From the confluence of the sinuses, blood was passed through a previously calibrated electromagnetic flow probe, before being returned to the dog via the femoral vein. With this technique approximately 50–70% of the mass of the brain is drained at the confluence of the sagittal and straight sinuses (Rapela and Green, 1964). Cerebral venous outflow pressure was measured upstream from the flow probe. The venous outflow pressure was maintained near 0 mm Hg by manipulation of the reservoir level. This pressure measures the resistance to the flow of blood induced by the flow transducer, because the outflow cannula was set at the level of the right atrium and all pressures were referred to this common zero reference plane. Brain perfusion pressure was estimated as systemic arterial pressure minus cerebral venous outflow pressure. Intracranial vascular resistance was calculated by dividing brain perfusion pressure by cerebral venous outflow.

The verification of the measurement of CBF utilizing this venous outflow technique has been described in detail elsewhere (Traystman and Rapela, 1975); the viability and reactivity of the cerebral vasculature to hypercapnia (Traystman and Rapela, 1975), hypoxia (Traystman, Fitzgerald and Loscutoff, 1978; Traystman and Fitzgerald, 1981) and ability to autoregulate (Rapela and Green, 1964) using this technique has been previously demonstrated. In the absence of increased venous outflow pressures (>2 mm Hg), this method of CBF measurement compares favourably with CBF measured by the injection of microspheres (Wagner and Traystman, 1983).

Hypoxia and hypercapnia, and blood-gas analysis

Arterial hypoxia was produced through decreasing arterial oxygen content by introducing a gas mixture containing 6.5% oxygen and 93.5% nitrogen to the inspiratory limb of the respirator. Arterial carbon dioxide tension was maintained constant throughout. Hypoxia was maintained for 10–15 min to allow for measurement under near steady-state conditions. The CBF response to hypercapnia was evaluated by introducing likewise a carbon dioxide-containing gas mixture. Five and 10 percent carbon dioxide in air were utilized as the gas mixtures, and hypercapnia was maintained for 10 min at each concentration so that near steady-state measurements could be obtained.

Arterial and cerebral venous blood samples were taken directly from the femoral artery and cerebral venous outflow cannulae, respectively. The design of the study was such that each dog acted as its own control for hypoxia and hypercapnia. Arterial oxygen tension (Pa_{O_2}), carbon dioxide tension (Pa_{CO_2}) and pH were measured at 37 °C immediately after the withdrawal of the samples (Radio-

TABLE I. *Haemodynamic, blood-gas, and pH data in each group of animals. Group 1 was anaesthetized initially with pentobarbitone 30 mg kg^{-1} i.v. and then received alfentanil 0.32 mg kg^{-1} i.v. Group 2 animals were anaesthetized initially with pentobarbitone 30 mg kg^{-1} i.v. and the effects of hypoxia and hypercapnia were studied. Group 3 animals were initially anaesthetized with alfentanil 0.32 mg kg^{-1} i.v. plus pentobarbitone 1–2 mg kg^{-1} and anaesthesia maintained with an alfentanil infusion 0.32 mg kg^{-1} h^{-1} i.v. and the responses to hypoxia and hypercapnia were studied. MAP = mean arterial pressure; CBF = cerebral blood flow; CVR = cerebral vascular resistance;* Pa_{O_2} *= arterial oxygen tension;* Pa_{CO_2} *= arterial carbon dioxide tension;* Ca_{O_2} *= arterial oxygen content;* $CMRo_2$ *= cerebral oxygen consumption. Each value represents the mean ± SEM.* *$P < 0.05$ *compared with control,* †$P < 0.05$ *compared with group 2*

	MAP (mm Hg)	CBF (ml min^{-1})	CVR (mm Hg ml^{-1} min^{-1})	pH	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	Ca_{O_2} (ml dl^{-1})	CMRo$_2$ (ml min^{-1})
Group 1 ($n = 6$)								
Pre-alfentanil	115±10	30±3	4.1±0.6	7.41±0.01	12.5±0.93	3.9±0.27	16.2±0.9	2.28±0.32
Post-alfentanil	78±11*	29±3	2.7±0.3*	7.41±0.01	12.1±0.8	3.9±0.13	15.9±1.0	2.37±0.39
Group 2 ($n = 5$)								
Control	97±7	27±2	3.7±0.4	7.44±0.02	12.6±1.1	4.4±0.27	15.6±0.9	1.91±0.09
Hypoxia	149±5*	77±11*	2.1±0.4*	7.49±0.02*	3.2±0.13*	4.0±0.13	4.4±0.5*	1.78±0.17
Control	104±6	25±2	4.1±0.5	7.42±0.02	12.1±0.9	4.1±0.27	16.2±0.8	1.83±0.14
5% CO$_2$	103±5	41±6*	2.7±0.05*	7.27±0.02*	12.4±81.1	6.7±0.4*	16.1±0.8	1.84±0.20
10% CO$_2$	102±6	63±5*	1.7±0.2*	7.15±0.02*	12.9±70.9	9.2±0.7*	17.1±1.1	1.55±0.22*
Group 3 ($n = 6$)								
Room air	105±5	36±3	3.0±0.3	7.40±0.01†	12.1±0.5	4.5±0.27	15.5±1.2	2.40±0.10
Hypoxia	180±16*	111±13*†	1.6±0.2*	7.41±0.02†	2.4±0.13*	4.5±0.27	3.8±0.4*	1.67±0.18*
Control	109±11	37±3	3.0±0.4	7.39±0.01	12.2±0.9	4.7±0.13	16.0±1.6	2.50±0.11
5% CO$_2$	114±13	52±5*	2.3±0.4*	7.27±0.02*	12.5±0.9	6.3±0.27 *	15.6±1.2	1.99±0.09*
10% CO$_2$	113±14	76±1*	1.7±0.4*	7.16±0.01*	12.0±0.9	8.9±0.27 *	15.5±1.3	1.59±0.14*

meter BMS3). The electrodes were calibrated with air (20.8% oxygen), and mixtures of oxygen in nitrogen (8%) and 5 and 10% carbon dioxide in air were analysed to a precision of 0.1%. The pH electrode was calibrated with standard phosphate buffers (6.840; 7.381). Oxygen saturation and haemoglobin were measured also immediately after sampling (Instrumentation Laboratories Co-oximeter Model 282). Electrodes were calibrated before and after each set of samples. Arterial and venous oxygen content were calculated from the measured oxygen saturation and haemoglobin concentration. CMRo$_2$ was calculated by multiplying CBF by the arterial to cerebro–venous oxygen content difference.

CBF autoregulation limits were also examined. Autoregulation in these studies was defined as the ability of the brain to maintain constant CBF despite wide variations in arterial pressure. The lower limit of cerebral autoregulation was determined by removal of blood from the femoral artery in 100-ml increments. A stabilization period of approximately 2 min was allowed after the removal of each aliquot of blood. As we were able to monitor CBF continuously, we were able to determine readily the stability of the CBF. In every instance, CBF was constant during the times immediately before and after the determination of CBF. The lower limit of autoregulation was determined visually as the mean arterial pressure at which CBF did decrease with a decrease in arterial pressure. In most animals, 600–1000 ml of blood was removed, and the determination of the lower limit of autoregulation usually required 20 min. The upper limit of cerebral autoregulation was determined by increasing mean arterial pressure in 20-mm Hg increments (noradrenaline 4 µg ml^{-1}) and maintaining that value for approximately 2 min. The upper limit of autoregulation was determined visually as the mean arterial pressure at which CBF increased with an increase in arterial pressure. Generally this procedure was completed within 20 min.

Plan of investigation and data analysis

The direct effect of alfentanil 0.32 mg kg^{-1} i.v. on CBF and CMRo$_2$ was studied in group 1 animals ($n = 6$) anaesthetized with pentobarbitone 30 mg kg^{-1} i.v. In group 2 animals ($n = 5$) anaesthetized with pentobarbitone 30 mg kg^{-1} i.v. and in group 3 animals anaesthetized with alfentanil 0.32 mg kg^{-1} i.v. plus pentobarbitone 1–2 mg kg^{-1} i.v. and a continuous infusion of alfentanil 0.32 mg kg^{-1} h^{-1}, the responses to

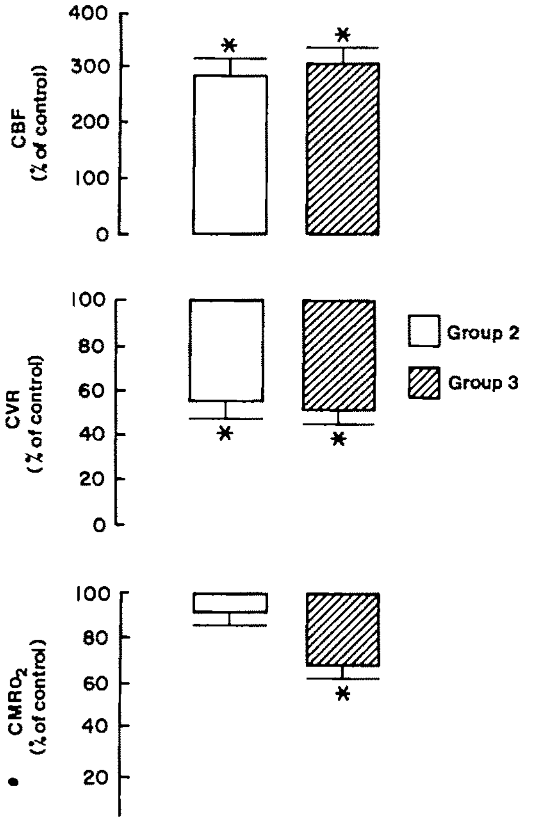

FIG. 1. Responses of cerebral blood flow (CBF), cerebral vascular resistance (CVR) and cerebral oxygen consumption (CMR_{O_2}) to hypoxia in groups 2 and 3. Group 2 animals were anaesthetized with pentobarbitone 30 mg kg^{-1} i.v. and group 3 animals were anaesthetized with alfentanil 0.32 mg kg^{-1} i.v. plus pentobarbitone 1–2 mg kg^{-1} i.v. and a continuous infusion of alfentanil 0.32 mg kg^{-1} h^{-1}. Each bar represents the mean ± SEM. *$P < 0.05$.

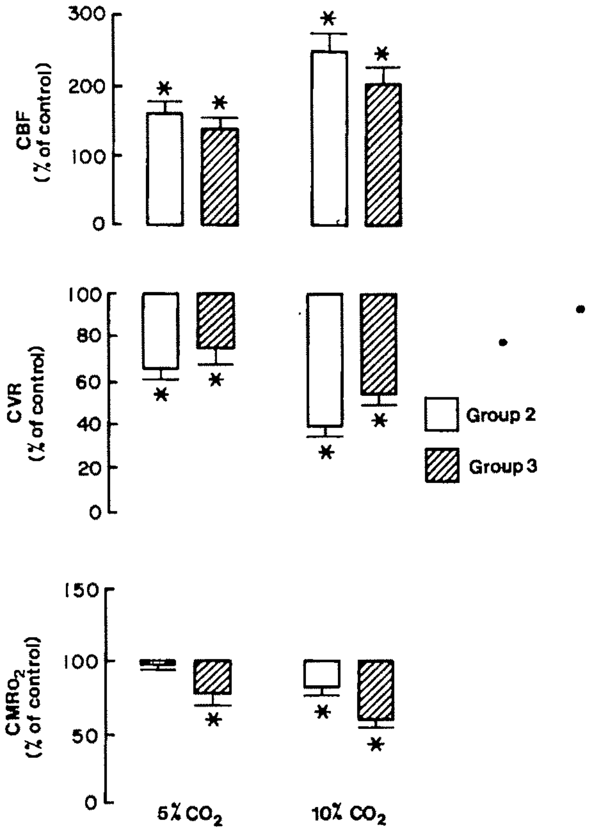

FIG. 2. Responses of cerebral blood flow (CBF), cerebral vascular resistance (CVR) and cerebral oxygen consumption (CMR_{O_2}) to two levels of hypercapnia are shown. Group 2 animals were initially anaesthetized with pentobarbitone 30 mg kg^{-1} i.v. and group 3 animals were anaesthetized with alfentanil 0.32 mg kg^{-1} i.v. plus pentobarbitone 1–2 mg kg^{-1} i.v. and continuous infusion of alfentanil 0.32 mg kg^{-1} h^{-1}. Each bar represents the mean ± SEM. *$P < 0.05$.

hypoxia, hypercapnia and the upper and lower limits of cerebral autoregulation were determined. Within groups 2 and 3, the order of interventions was randomized and the animals were allowed a stabilization period (about 15 min) between each intervention.

In group 1, findings before and after the injection of alfentanil were evaluated using a paired Student's *t* test. In groups 2 and 3, statistical analysis was performed using analysis of variance (Human Systems Dynamics, Northridge, California) for between–within variables for hypoxia, hypercapnia and limits of autoregulation. $P < 0.05$ was considered significant. All values in text and figures are shown as mean ± SEM.

RESULTS

Haemodynamic, blood-gas and pH changes for all groups of animals are presented in table I. In group 1, alfentanil 0.32 mg kg^{-1} i.v. decreased mean arterial pressure (MAP) to 68% of control 2 min following injection. CBF and CMR_{O_2} remained unchanged from their control values, whereas cerebral vascular resistance (CVR) had decreased to 66% of control 2 min following the injection.

In the animals in group 2, Pa_{O_2} was decreased from 12.6 ± 1.1 to 3.2 ± 0.13 kPa, and CBF increased to 285% of control and CVR decreased to 57% of control. In group 3, as Pa_{O_2} was decreased from 12.1 ± 0.5 to 2.4 ± 0.13 kPa, CBF increased to 308 % of control and CVR decreased to 53 % of control. The CBF response to hypoxia was greater in group 3 compared with group 2 animals; however, the Pa_{O_2} and arterial oxygen content were also lower in group 3. CMRo$_2$ was unchanged from control in group 2, but was decreased to 70 % of control in group 3, with the more severe hypoxia.

In group 2 as arterial carbon dioxide tension (Pa_{CO_2}) was increased from 4.1 ± 0.27 to 6.7 ± 0.4 and then to 9.2 ± 0.67 kPa, CBF increased to 152 and 252 % of control, respectively, and CVR decreased to 66 and 41 % of control, respectively. Both pH and CMRo$_2$ were reduced significantly. In group 3, as Pa_{CO_2} was increased from control (4.7 ± 0.13 to 6.3 ± 0.27) kPa and then to 8.9 ± 0.27 kPa, CBF increased to 141 and 209 % of control, respectively, and CVR decreased to 77 and 57 % of control, respectively. As in group 2, pH and CMRo$_2$ decreased significantly with hypercapnia.

Figure 1 shows the response of CBF, CVR, and CMRo$_2$ to hypoxia in group 2 animals anaesthetized with pentobarbitone and group 3 animals anaesthetized with alfentanil (plus small amounts of barbiturate). With both basal anaesthetics, the CBF increased to approximately 300 % of control during hypoxia while the CVR decreased to about 60 % of control. CMRo$_2$ was unchanged in group 2 animals anaesthetized with barbiturate, but was decreased in group 3 animals anaesthetized with alfentanil plus small amounts of barbiturate. Figure 2 shows the response of CBF, CVR and CMRo$_2$ to hypercapnia in animals anaesthetized with barbiturate (group 2) and alfentanil (group 3). Five and 10 percent carbon dioxide increased CBF by approximately 175 and 250 % of control, respectively. CVR decreased to about 75 % and 50 % of control in both groups and CMRo$_2$ was decreased in both groups by hypercapnia. CMRo$_2$ was unchanged from control in group 2 animals at the lower Pa_{CO_2} value.

The upper and lower limits of cerebral autoregulation were determined in group 2 animals anaesthetized with barbiturate and group 3 animals anaesthetized with alfentanil plus small amounts of barbiturate. The lower and upper limits of autoregulation in group 2 were 48 ± 5 and 182 ± 7 mm Hg, respectively. The limits of autoregulation in group 3 were 46 ± 5 and 190 ± 3 mm Hg and these limits were not different from group 2 animals anaesthetized with barbiturate.

DISCUSSION

In this study, the cerebral venous outflow technique (Rapela and Green, 1964), in which transient changes in CBF could be monitored continuously, was used and the response of CBF and CMRo$_2$ to any intervention observed. While one advantage of this technique is that it measures CBF nearly devoid of extracerebral contamination, a disadvantage of this model is the need for anaesthesia during the surgical preparation. Therefore, we have no observation of the effects of alfentanil in the unanaesthetized animal. Baseline CBF in this study was similar to our recent study of fentanyl (McPherson and Traystman, 1984), but was somewhat higher than those previously reported (Traystman, Fitzgerald and Loscutoff, 1978; Traystman and Fitzgerald, 1981). As in our previous study (McPherson and Traystman, 1984), control CBF was around 30 ml min^{-1}, whereas in the earlier studies control flows were 20–23 ml min^{-1}. Basal CBF in this study was at a lower baseline arterial oxygen content (15 vol %), whereas in previous studies, baseline arterial oxygen content was about 19 vol % and CBF was somewhat lower. In fact, a CBF of 30 ml min^{-1} at an arterial oxygen content of 15 % vol %, is consistent with our previous studies of the effect of decreased arterial oxygen content on CBF (Traystman, Fitzgerald and Loscutoff, 1978; Traystman and Fitzgerald, 1981).

Alfentanil 0.32 mg kg^{-1} i.v., a dose twice that shown to cause profound analgesia and anaesthesia in both animals and man (Nauta et al., 1983), did not alter CBF despite a substantial decrease in MAP (40 mm Hg). An advantage of the venous outflow technique is the ability to observe transient changes in CBF. Observations were made immediately after the administration of the alfentanil and, although CBF was unchanged, CVR decreased significantly. This was a consequence of the decreased MAP and unchanged CBF and suggests that the decrease in CVR was a normal adjustment to maintain CBF constant in response to a decrease in MAP within the autoregulation range.

We studied the effect of alteration in MAP on CBF using haemorrhagic hypotension and noradrenaline-induced hypertension. Noradrenaline has been shown not to cross the blood–brain barrier and thus has no direct cerebral vascular effect when given i.v. (O'Neill and Traystman, 1977). The limits of autoregulation were similar to those reported by others (Rapela and Green, 1964) and in our previous study of fentanyl (McPherson and Traystman, 1984). These data suggest that increases in CBF in the presence of alfentanil and small amounts of barbiturates would be less with hypertension than that noted in the presence of inhalation agents, which have been shown to decrease the ability of cerebral vessels to autoregulate in a dose-dependent manner (Miletich et al., 1976; Morita et al., 1977; Todd and Drummond, 1984).

The lower limit of autoregulation found in this study was also comparable to those reported previously (Rapela and Green, 1964; McPherson and Traystman, 1984). CVR was decreased to a similar value in animals anaesthetized with barbiturate and animals anaesthetized with alfentanil plus small amounts of barbiturate, and the CBF was unchanged. This suggests that alfentanil plus small doses of barbiturate does not interfere with maintenance of CBF at relatively low arterial pressures. Thus these data suggest that alfentanil anaesthesia would be an acceptable anaesthetic in situations in which cerebral perfusion pressure is low, such as hypovolaemic hypotension or carotid surgery.

We have demonstrated an essentially linear increase in CBF with increases in Pa_{CO_2} in animals anaesthetized with alfentanil and small doses of barbiturate which did not differ from the effect in animals anaesthetized with barbiturate only. This differs from situations when anaesthetic doses of anaesthetic gases are administered, in which the CBF response to carbon dioxide is altered (Miletich et al., 1976). These data suggest that alfentanil anaesthesia would allow manipulation of ICP by inducing alterations in Pa_{CO_2}.

Hypercapnia resulted in a decrease in $CMRo_2$ in both barbiturate- and alfentanil-anaesthetized animals. This decrease in $CMRo_2$ occurs in anaesthetized but not sedated animals (Berntmann and Dahlgren, 1979). The mechanism of maintenance of $CMRo_2$ in unanaesthetized animals was considered to be an increased catecholamine turnover as a result of hypercapnia and a resultant increase in $CMRo_2$. Both anaesthesia and propranolol have been shown to prevent the increase in $CMRo_2$ caused by hypercapnia (Berntmann and Dalgren, 1979); the mechanism of the decrease in $CMRo_2$ remains unclear.

CBF increased in response to hypoxia both in animals anaesthetized with barbiturate and animals anaesthetized with alfentanil. CBF increased to 3 times control during hypoxia in both groups; however, $CMRo_2$ was not decreased by hypoxia in animals anaesthetized with barbiturate only. $CMRo_2$ was decreased during hypoxia in animals anaesthetized with alfentanil. This occurred because the Pa_{O_2} and arterial oxygen content were decreased more in the alfentanil-anaesthetized animals than in barbiturate-anaesthetized animals, and the CBF response in those animals was insufficient to offset the reduction in oxygen delivery. These data suggest that alfentanil plus small doses of barbiturate is not different from moderate doses of barbiturate in its lack of adverse affects on the cerebral hypoxic response.

In summary, our data demonstrate that high-dose alfentanil in the presence of small doses of pentobarbitone does not alter cerebral haemodynamic responses to hypoxia or hypercapnia. In addition, the lower and upper limits of autoregulation are not altered by alfentanil. Since the normal cerebral compensatory mechanisms appears to be intact with high doses of alfentanil and since there is a well documented cardiovascular stability with alfentanil, this suggests that high doses of alfentanil would be an acceptable anaesthetic technique in neurosurgical patients.

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A SHEEP PREPARATION FOR STUDYING INTERACTIONS BETWEEN BLOOD FLOW AND DRUG DISPOSITION.

IV: THE EFFECTS OF GENERAL AND SPINAL ANAESTHESIA ON BLOOD FLOW AND CEFOXITIN DISPOSITION

W. B. RUNCIMAN, L. E. MATHER, A. H. ILSLEY, R. J. CARAPETIS AND R. N. UPTON

SUMMARY

Control measurements of blood flow through and cefoxitin extraction ratios across heart and lungs, liver, kidneys and gut were made under steady-state conditions in awake unrestrained sheep. The studies then were repeated with the same animals anaesthetized with 1.5% halothane or whilst undergoing high thoracic (to approximately T4) subarachnoid blockade with amethocaine. In the control-drug studies, it was shown that cefoxitin was cleared by the kidneys and that the cefoxitin infusion produced no significant changes in haemodynamics or in the kinetics of iodohippurate (the marker substance used for determining renal blood flow). Under general anaesthesia, there were significant reductions in renal blood flow (to 61% of the mean control value), in iodohippurate renal extraction ratio and clearance (to, respectively, 64 and 38% of the mean control values) and in cefoxitin renal extraction ratio and clearance (to, respectively, 48 and 23% of the mean control values). Under spinal anaesthesia there were no significant changes in haemodynamics or in cefoxitin or iodohippurate extraction ratios or clearances.

Since general and spinal anaesthesia may have effects on the cardiovascular system (Prys-Roberts, 1980; Greene, 1981), it was decided to study such effects in conjunction with studies of the disposition of selected drugs with potentially flow-limited clearance, using sheep with chronically implanted catheters (Runciman et al., 1984a, b). In this paper, studies on the disposition of cefoxitin are presented. Cefoxitin sodium is a broad spectrum, bactericidal, semi-synthetic antibiotic with a wide margin of safety which has been found useful in peri-operative care (Brogden et al., 1979; Schrogie et al., 1978). It has a high renal clearance, minimal cardiovascular effects, and does not affect renal function (Brogden et al., 1979). Since the clearance of cefoxitin by the kidney depends on energy-dependent processes (tubular secretion) and renal blood flow, it is useful as a probe with which the effects of anaesthesia on the disposition of a drug cleared by the kidneys may be studied.

MATERIALS AND METHODS

Design of study

The studies into the effects of general and spinal anaesthesia on haemodynamics and cefoxitin disposition were carried out in sheep according to standard procedures developed to study, concurrently, interactions between blood flow and drug disposition. The rationale for the choice of species, the preparation of the animals for study, and the demonstration of the maintenance of normal physiological function over the study period, have been presented previously (Runciman et al., 1984a, b). However, a brief description of those

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TABLE I. *Cefoxitin infusion rates in the control-drug (C), general (GA) and spinal anaesthesia (SA) studies*

Study	C1	GA1	C2	GA2	C3	GA3	Ci	SAi	Cii	SAii	Ciii	SAiii
Loading infusion for 15 min (mg min^{-1})	9.9	10.0	10.0	9.9	10.9	10.9	21.0	21.4	21.0	21.4	9.9	10.9
Maintenance infusion for 75 min (mg min^{-1})	4.0	4.0	4.0	4.0	4.4	4.4	8.4	8.6	8.4	8.0	4.0	4.4

aspects pertaining to the studies of cefoxitin disposition is presented here.

Sheep were acclimatized to being in metabolic crates and then, under general anaesthesia, multiple intravascular catheters were placed, including a left renal vein catheter placed via the right jugular vein, and aortic catheters placed via the right carotid artery. On recovery, the catheters were attached to a flushing system and 2 weeks was allowed for the sheep to recover from the procedure. Cardiac output was measured by thermodilution, and renal blood flow by the Fick method using sodium ^{125}I-iodohippurate (IOH) (Runciman et al., 1984a). By simultaneously sampling from the aortic and renal vein catheters, renal blood flow and IOH and cefoxitin renal extraction ratios could be measured repeatedly.

Three studies in sheep under 1.5% halothane general anaesthesia (studies designated GA1–GA3) were each compared with control-drug studies in the same animals awake (C1–C3) and three studies in sheep under high thoracic spinal anaesthesia (to approximately T4) (SAi–SAiii) were each compared with control-drug studies in the same animals (Ci–Ciii). The details of each investigation have been described previously in detail (Runciman et al., 1984c), but pertinent aspects are repeated below. In each control-drug study, control measurements of cardiac output, renal blood flow, arterial pressure, and heart rate were obtained every 10 min for 60 min (seven sets). Cefoxitin sodium was then infused to the right atrium using a two-stage infusion (table I) designed to achieve steady-state conditions rapidly. Arterial samples were taken every 5 min for 30 min after the start of the 15-min cefoxitin loading infusion, every 10 min during the 75-min maintenance infusion and every 5 min for 30 min after the cessation of the maintenance infusion. Blood samples from the other sites (including renal vein) were taken every 10 min immediately after the haemodynamic measurements during, and for 30 min after, the drug infusions (12 sets). The last 60-min period of the cefoxitin infusion was regarded as a "steady-state" period for comparison of haemodynamic data with those obtained in the control period before cefoxitin infusion.

In each general anaesthesia study, the control period was shortened to four sets of measurements obtained 10 min apart, anaesthesia was induced with thiopentone sodium 20 mg kg^{-1} i.v., a cuffed endotracheal tube was inserted, and anaesthesia maintained with 1.5% halothane in 40% oxygen (balance nitrogen). A constant volume ventilator provided intermittent positive pressure ventilation. The vaporizer and ventilator were adjusted to maintain expired halothane concentrations at 1.5% and expired carbon dioxide concentrations at 5%. After the induction of anaesthesia, the sheep was placed in its "normal" lying position with its legs tucked comfortably beneath it. The sternum and forelegs were supported on a foam rubber bolster so that the abdomen was not subject to compression. After 60 min, cefoxitin was infused and measurements made using a regimen identical to the control-drug study. Saline (0.9%, up to a total of 200 ml), was infused i.v. as required; mean arterial pressure was maintained within 5% of control values during the cefoxitin infusion. The last 60-min period of the cefoxitin infusion was regarded as a "steady-state" period for comparison of haemodynamic data with those obtained in the control period before the GA.

In each spinal anaesthesia study, four sets of control measurements were made, as in the general anaesthesia studies. After skin preparation, a 20-gauge spinal needle was inserted to the subarachnoid space in the lumbar region and 1% amethocaine hydrochloride 5 ml was injected over 5 s with barbotage. Saline (0.9%, up to a total of 200 ml) was infused i.v. at this stage; the mean arterial pressure was maintained within 1% of control values during the cefoxitin infusion. The subarachnoid blockade was allowed to stabilize for 30 min and the posture of the sheep was adjusted as in the general anaesthesia studies. The level of blockade was monitored by observing reflex flicking of the skin in response to prodding with a finger (Lebeaux, 1975). After 60 min, cefoxitin was infused and measurements were made accord-

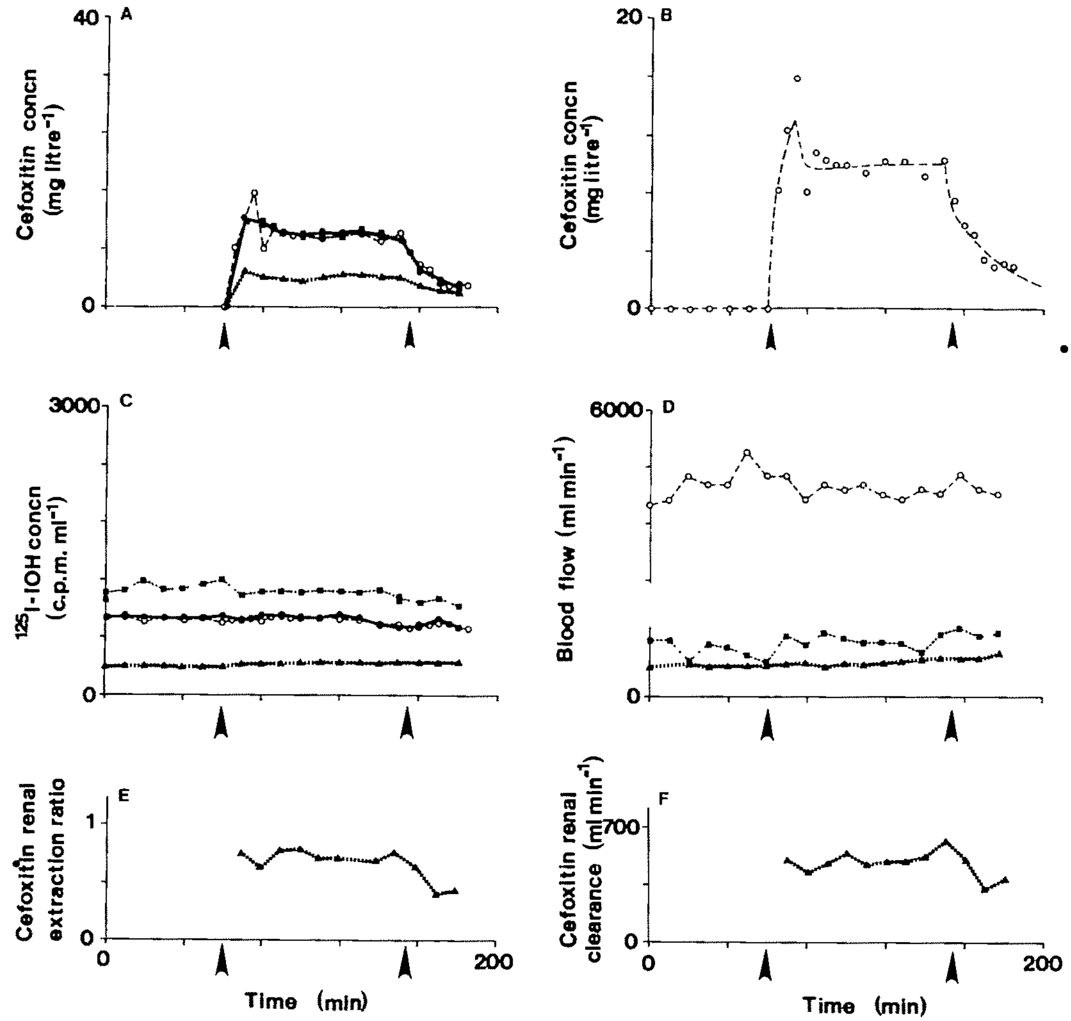

FIG. 1. A typical cefoxitin control-drug study (C2). A: Cefoxitin blood concentrations; note the substantial arterial–renal vein cefoxitin concentration differences. B: Bi-exponential curve fit to cefoxitin arterial concentration–time data. In this study, the mean total body clearance (dose divided by area under the curve in this panel) was within 3% of the mean directly measured renal clearance (see panel F). C: ^{125}I-iodohippurate (IOH) blood concentrations from mesenteric vein infusion. Hepatic vein–arterial and arterial–renal vein concentration differences divided into the dose rate represent hepatic and renal blood flows, respectively. D: Total arterial blood flow (cardiac output), hepatic and renal blood flows. Note the lack of haemodynamic effects of the cefoxitin infusion. E: Cefoxitin renal extraction ratios (derived from the data in panel A). F: Cefoxitin renal clearances (derived from the products of the paired extraction ratios in panel E and renal blood flows in panel D). ○—○ = Arterial; ●——● = pulmonary; ■—■ = hepatic; ▲┈▲ = renal. The arrows denote the beginning and ending of the cefoxitin infusion.

ing to the regimen used in the control-drug and general anaesthesia studies. The blockade did not start to regress until 160 min had elapsed, but had always started to regress by 180 min. The last 60-min period of the cefoxitin infusion was regarded as a "steady-state" period for comparison of haemodynamic data with those obtained in the control period before the SA.

The haemodynamic and IOH kinetic parameters during the "steady-state" period in each general anaesthesia and spinal anaesthesia study were each expressed as a percentage of the mean value of the

TABLE II. *Effects of cefoxitin on blood flow and iodohippurate kinetics in awake animals. Values for cardiac output (CO), renal blood flow (RBF), iodohippurate renal extraction ratio (IOH ER) and directly measured iodohippurate clearance (IOH Cl) before the cefoxitin infusion in the control-drug studies (C) may be compared with those during the last 60 min of the cefoxitin infusion*

		Before cefoxitin infusion (7 sets of determinations, 10 min apart over 60 min)				During cefoxitin infusion (7 sets of determinations, 10 min apart over 60 min)			
		CO (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})	CO (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})
C1	Mean	4.30	0.59	0.62	0.36	4.50	0.59	0.60	0.36
	SD	0.50	0.04	0.04	0.01	0.30	0.04	0.01	0.01
C2	Mean	4.00	0.65	0.63	0.41	3.90	0.72	0.57	0.36
	SD	0.40	0.04	0.02	0.01	0.10	0.05	0.02	0.01
C3	Mean	4.20	0.88	0.65	0.56	4.60	0.87	0.62	0.54
	SD	0.20	0.13	0.09	0.01	0.30	0.05	0.02	0.01
Ci	Mean	4.80	0.69	0.82	0.56	5.00	0.69	0.76	0.53
	SD	0.20	0.03	0.02	0.02	0.60	0.06	0.01	0.04
Cii	Mean	4.90	0.56	0.76	0.43	5.70	0.52	0.74	0.38
	SD	0.40	0.03	0.04	0.02	0.06	0.01	0.01	0.01
Ciii	Mean	4.50	0.56	0.72	0.40	4.50	0.62	0.69	0.42
	SD	0.30	0.03	0.02	0.02	0.40	0.04	0.02	0.02

corresponding parameter on that day in the same animal, during the control period preceding the drug infusion, and were compared using Student's *t* test. As the effects of general and spinal anaesthesia on regional blood flow and oxygen tensions have been reported separately (Runciman et al., 1984c), only those haemodynamic changes which directly affect the measurement or interpretation of the disposition of cefoxitin are reported in detail in this paper.

Cefoxitin analysis and disposition

Cefoxitin blood concentrations were determined after separation of plasma and acetonitrile precipitation of the soluble proteins. The concentrations were read from standard curves prepared after spiking whole blood with known amounts of cefoxitin and an internal standard (cephamandole) and assayed at the same time. A high pressure liquid chromatographic technique was used with a C18 reverse phase column and a mobile phase consisting of 25% methanol and 75% acetic acid (0.5% in water). At a mobile phase flow rate of 2 ml min^{-1}, the retention times of cefoxitin and cephamandole were, respectively, 3.6 and 5.0 min. All drug amounts and concentrations were expressed as the sodium salt.

Cefoxitin clearances by kidney, liver, gut and lungs were determined from the products of blood flow through and extraction ratio across the relevant organs during the steady-state period. Arterial cefoxitin blood concentration–time data were used in conjunction with a non-linear least squares regression method to derive the parameters of a polyexponential equation (Mather, Ringrose and Austin, 1982), from which the mean total body clearance was calculated from the ratio of dose to area under the arterial concentration–time curve (Hull, 1979). The disposition parameters of cefoxitin during each general and spinal anaesthesia study were each expressed as percentages of the mean value of the corresponding parameter during the control-drug study in the same animal, and were compared using Student's *t* test for paired data.

RESULTS

Control-drug studies

A set of results from a typical control-drug study is presented in figure 1; note that there was no detectable splanchnic, hepatic or pulmonary clearance of cefoxitin, but that there was substantial renal clearance. During the steady-state period of the cefoxitin infusion in the control-drug studies, the mean values for cardiac output, renal blood flow, renal fraction of cardiac output, IOH extraction ratio and IOH clearance, were all within 5% of their corresponding control values (table II); mean arterial pressure and heart rate remained within 3% of their control values. The mean total body clearance of cefoxitin derived from the curve-fit method in all the control-drug studies was 102 (SD 10) % of that derived directly from the products of the measured renal blood flow and cefoxitin renal extraction ratio.

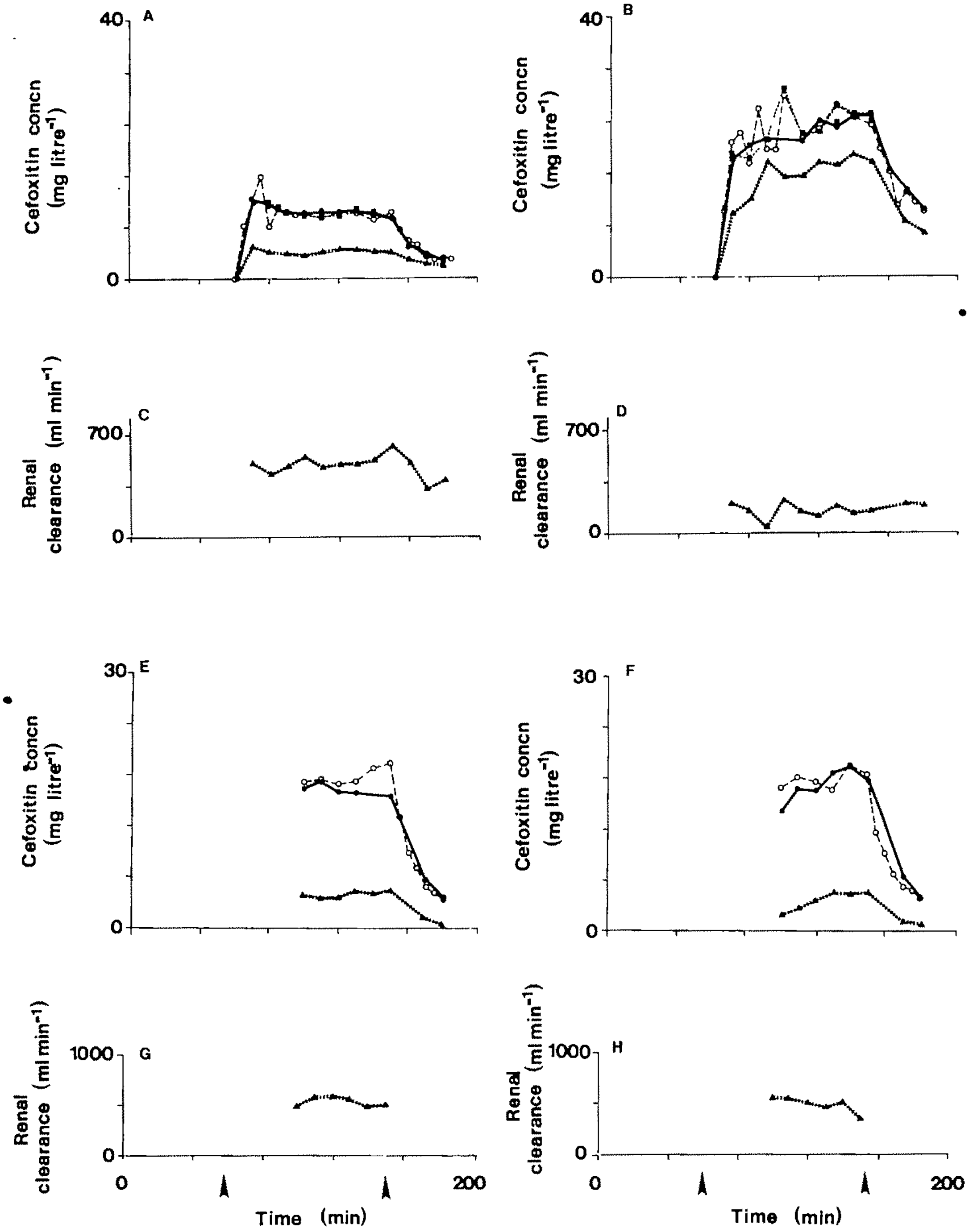

FIG. 2. Typical paired cefoxitin control-drug and anaesthesia studies (C2 and GA2; Ci and SAi). Blood concentrations of cefoxitin in panel A (C2) may be compared with those in panel B (GA2), and those in panel E (Ci) may be compared with those in panel F (SAi). Renal clearances of cefoxitin in panel C (C2) may be compared with those in panel D (GA2), and those in panel G (Ci) may be compared with those in panel H (SAi). ○—○ = Arterial; ●——● = pulmonary; ■--■ = hepatic; ▲···▲ = renal. The arrows denote the beginning and ending of the cefoxitin infusion.

TABLE III. *Effects of general anaesthesia on blood flow and iodohippurate kinetics. Values for cardiac output (CO), renal blood flow (RBF), iodohippurate renal extraction ratio (IOH ER) and directly measured iodohippurate renal clearance (IOH Cl) in the control period before general anaesthesia (GA) may be compared with those during the last 60 min of the cefoxitin infusion during general anaesthesia*

		Before general anaesthesia and cefoxitin infusion (4 sets of determinations, 10 min apart over 30 min)				During general anaesthesia and cefoxitin infusion (7 sets of determinations, 10 min apart over 60 min)			
		CO (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})	CO (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})
GA1	Mean	5.20	0.50	0.71	0.36	3.40	0.37	0.40	0.15
	SD	0.10	0.03	0.04	0.01	0.10	0.02	0.03	0.01
GA2	Mean	3.40	0.56	0.64	0.36	4.00	0.42	0.44	0.18
	SD	0.50	0.02	0.01	0.01	0.40	0.02	0.02	0.01
GA3	Mean	3.30	0.50	0.65	0.33	1.60	0.17	0.44	0.07
	SD	0.20	0.10	0.04	0.04	0.30	0.02	0.06	0.00

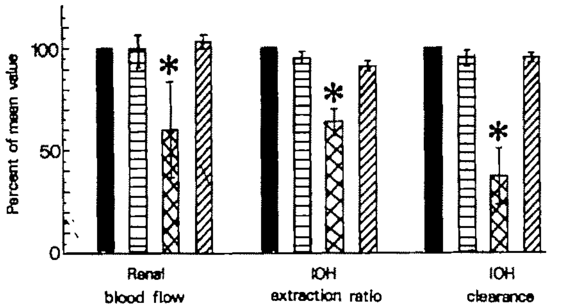

FIG. 3. Renal blood flow and IOH disposition. The mean values and standard deviations of renal blood flow, IOH extraction ratio and IOH clearance during the steady-state period of the control-drug (⊟), GA (☒) and SA (▨) studies were each expressed as percentages of the mean value of the corresponding parameter on that day in the same animal during the control period (■) preceding the drug infusion. $*P < 0.05$.

General anaesthesia studies

Typical effects of general anaesthesia on cefoxitin blood concentrations and renal clearance are shown in figure 2. Under general anaesthesia, there were significant reductions in renal blood flows, IOH extraction ratio and IOH clearance ($P < 0.05$, one tail test) (table III, fig. 3). Changes in other haemodynamic variables were all within 10% of those previously reported to occur under general anaesthesia in this preparation (Runciman et al., 1984c). Mean arterial pressure decreased from 92 to 88 mm Hg and mean heart rate increased from 121 to 126 beat min^{-1}.

Effects of general anaesthesia on cefoxitin disposition are presented in table IV, and a summary of the relevant results is presented in figure 4. Under general anaesthesia, arterial cefoxitin concentrations were 2.5–5-fold higher because renal extraction ratios and clearances were lower. In contrast to control-drug studies, arterial concentrations did not reach a steady-state, but continued to increase slightly throughout the maintenance infusion period. During the last 60 min of the maintenance infusion the cefoxitin renal extraction ratio and renal clearance under general anaesthesia decreased to mean values of 48 and 23%, respectively, of their corresponding values in the control-drug studies ($P < 0.05$, one tail test). Similarly, the mean total body clearance of cefoxitin decreased to a mean of 29% of the values obtained in the control-drug studies ($P < 0.01$, one tail test).

Spinal anaesthesia studies

All the haemodynamic and IOH kinetic variables measured during the cefoxitin steady-state period under spinal anaesthesia were within 10% of the corresponding mean values during the control period on that day (table V, fig. 3). Mean arterial pressure remained unchanged at 100 mm Hg, and mean heart rate decreased from 117 to 114 beat min^{-1}.

Typical results for cefoxitin blood concentrations and renal clearances during spinal anaesthesia are shown in figure 2.

Effects of spinal anaesthesia on cefoxitin disposition are presented in table VI and a summary of the relevant results is presented in figure 4. It is evident that no discernible changes occurred under spinal anaesthesia (mean values of cefoxitin renal extraction ratio and renal clearance were 93 and 99% of the values in the corresponding control-drug studies). Cefoxitin mean total body clearance under spinal anaesthesia was within 10% of its corresponding control value in the first

TABLE IV. *Effects of general anaesthesia on cefoxitin disposition. Values for cefoxitin renal extraction ratio (ER), directly measured cefoxitin renal clearance* (Cl), *mean arterial cefoxitin concentration (ARTC) and total body clearance (TBCl) during the last 60 min of the cefoxitin infusion in the control-drug studies (C) may be compared with those obtained in the same animal during the corresponding period in the general anaesthesia (GA) studies*

		Control-drug studies (7 determinations, 10 min apart over 60 min)						General anaesthesia studies (7 determinations, 10 min apart over 60 min)			
		ER	*Cl* (litre min^{-1})	ARTC (mg litre^{-1})	TB*Cl* (litre min^{-1})			ER	*Cl* (litre min^{-1})	ARTC (mg litre^{-1})	TB*Cl* (litre min^{-1})
C1	Mean	0.58	0.34	10.9	0.37	GA1	Mean	0.30	0.11	27.2	0.12
	SD	0.05	0.03	0.6	—		SD	0.05	0.03	2.8	—
C2	Mean	0.57	0.42	10.0	0.39	GA2	Mean	0.26	0.12	23.7	0.17
	SD	0.04	0.04	0.4	—		SD	0.05	0.03	2.8	—
C3	Mean	0.85	0.74	6.6	0.73	GA3	Mean	0.40	0.07	30.6	0.10
	SD	0.06	0.03	0.4	—		SD	0.01	0.02	3.9	—

study pair (Ci–SAi), but differed substantially in the next two paired control-drug and spinal anaesthesia studies. In the former case (SAii), this was the result of a poor curve fit and, in the latter case (SAiii), mean total body clearance may have been under-estimated by direct measurement of renal clearance.

DISCUSSION

In awake unrestrained animals, the infusions of cefoxitin produced no significant haemodynamic effects, and there was a good correlation between renal and mean total body clearances, confirming that cefoxitin clearance was taking place principally via the kidneys. This correlation was maintained under general and spinal anaesthesia.

Spinal anaesthesia produced no significant haemodynamic effects and no significant changes in IOH or cefoxitin clearances or extraction ratios. This was not unexpected, as mean arterial pressure was maintained by the infusion of physiological saline, and as autoregulation of renal blood flow has been shown to be well-maintained under spinal anaesthesia (Runciman et al., 1984c).

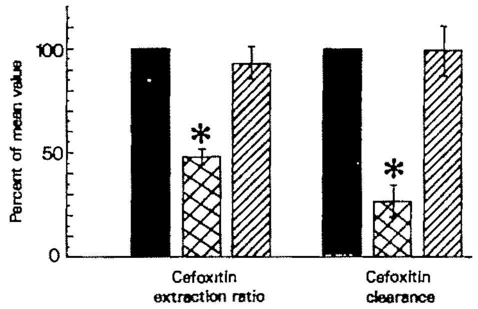

FIG. 4. Cefoxitin disposition. The mean values and standard deviations of cefoxitin extraction ratio and cefoxitin clearance during the steady-state period during GA (☒) and SA (▨) studies were each expressed as percentages of the mean value of the corresponding parameter in the control-drug study (■) in the same animal. $^*P < 0.05$.

TABLE V. *Effects of spinal anaesthesia on blood flow and iodohippurate kinetics. Values for cardiac output (CO), renal blood flow (RBF), iodohippurate renal extraction ratio (IOH ER) and directly measured iodohippurate renal clearance (IOH* Cl) *in the control period before spinal anaesthesia (SA) may be compared with those during the last 60 min of the cefoxitin infusion during spinal anaesthesia*

		Before spinal anaesthesia and cefoxitin infusion (4 sets of determinations, 10 min apart over 30 min)				During spinal anaesthesia and cefoxitin infusion (7 sets of determinations, 10 min apart over 60 min)			
		CO (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})	CO (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})
SAi	Mean	4.90	0.58	0.81	0.47	6.30	0.61	0.75	0.46
	SD	0.50	0.06	0.05	0.03	1.00	0.08	0.03	0.05
SAii	Mean	5.00	0.62	0.78	0.48	4.40	0.71	0.71	0.46
	SD	0.30	0.01	0.02	0.01	0.50	0.01	0.01	0.03
SAiii	Mean	3.10	0.62	0.69	0.43	4.10	0.63	0.64	0.40
	SD	0.08	0.05	0.01	0.03	0.10	0.08	0.04	0.03

TABLE VI. *Effects of spinal anaesthesia on cefoxitin kinetics. Values for cefoxitin renal extraction ratio (ER), directly measured cefoxitin renal clearance* (Cl), *mean arterial cefoxitin concentration (ARTC) and total body clearance (TBCl) for the last 60 min of the cefoxitin infusion in the control-drug (C) studies may be compared with those obtained in the same animal during the corresponding period in spinal anaesthesia (SA) studies*

Control-drug studies (7 sets of determinations, 10 min apart over 60 min)						Spinal anaesthesia studies (7 sets of determinations, 10 min apart over 60 min)					
		ER	*Cl* (litre min^{-1})	ARTC (mg litre^{-1})	TB*Cl* (litre min^{-1})			ER	*Cl* (litre min^{-1})	ARTC (mg litre^{-1})	TB*Cl* (litre min^{-1})
Ci	Mean	0.77	0.53	17.9	0.48	SAi	Mean	0.78	0.48	17.7	0.52
	SD	0.02	0.04	0.9	—		SD	0.05	0.07	1.2	—
Cii	Mean	0.87	0.50	15.4	0.58	SAii	Mean	0.80	0.51	20.7	0.37
	SD	0.01	0.02	0.7	—		SD	0.02	0.04	0.7	—
Ciii	Mean	0.78	0.48	8.7	0.43	SAiii	Mean	0.81	0.52	6.1	0.77
	SD	0.10	0.07	0.9	—		SD	0.04	0.07	1.1	—

The effects of general anaesthesia on renal blood flow were profound. There was a significant reduction in the renal fraction of cardiac output which, with the significant decrease in renal vein oxygen tension already reported in this preparation (Runciman et al., 1984c), suggests that autoregulation of renal blood flow is impaired under general anaesthesia despite the maintenance of mean arterial pressure. Furthermore, renal extraction ratio of IOH decreased significantly under general anaesthesia to a mean of 64% of the corresponding control value. Thus errors in methods for measuring renal blood flow which assume a constant extraction ratio of a marker substance used even in tracer quantities (Runciman et al., 1984a) may be compounded under general anaesthesia.

The fact that the arterial blood concentrations of cefoxitin increased substantially under general anaesthesia may have implications for drug dose regimens in the immediate postoperative period. Further studies have indicated that, although renal blood flow has returned to normal within 30 min of the end of anaesthesia, the depression of the energy-dependent renal tubular secretory processes may persist for several hours (Selby et al., 1984). Although cefoxitin has a high margin of safety, the potential for producing toxic responses with drugs having low margins of safety should be considered.

Thus, general anaesthesia, in contrast to spinal anaesthesia, may interfere with the autoregulation of renal blood flow, decrease the functional reserve for renal oxygenation, and depress some renal tubular secretory mechanisms, providing the potential for toxic drug concentrations and rendering invalid renal blood flow measurements which assume a constant extraction ratio of a marker substance. Studies on the effects of various inhalation and i.v. general anaesthetic agents and on the effects of spinal anaesthesia on the renal, hepatic, pulmonary and extra-visceral clearance (Runciman et al., 1984b) of other drugs will be the subjects of further reports.

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MIXTURES OF INHALATION AND I.V. ANAESTHETICS AT HIGH PRESSURE*

A Test of the Multi-Site Hypothesis of General Anaesthesia

B. WARDLEY-SMITH AND M. J. HALSEY

SUMMARY

We have tested the hypothesis that anaesthetics having different pressure reversal characteristics act at different molecular sites with finite capacities and, therefore, do not necessarily have additive potencies when used in mixtures of varying composition. The additivity of the anaesthetic potencies has been tested at normal pressures and at pressures up to 100 ATA for eight combinations of the following mixtures: Althesin plus nitrous oxide; methohexitone plus nitrous oxide; thiopentone plus nitrous oxide; thiopentone plus propanidid. The anaesthetic potencies of the first two mixtures were not additive at increased pressures, whereas those of the latter two mixtures were additive. These data support the multi-site hypothesis of general anaesthesia.

In 1978 an hypothesis was proposed for the mechanism of general anaesthesia which encompassed all the available data concerning pressure reversal of anaesthesia and was termed the multi-site expansion hypothesis of anaesthetic action (Halsey, Wardley-Smith and Green, 1978). This hypothesis retained some of the concepts of the original critical volume hypothesis (Lever et al., 1971) (namely, that anaesthetics expand and high pressure compresses a molecular site), but differed from it in a number of fundamental ways. Its tenets include:

(1) General anaesthesia can be produced by anaesthetic interactions at more than one type of *molecular* site: the critical site (or sites) varying between agents.

(2) These molecular sites do not behave as bulk solvents, but instead have a finite size and a limited capacity for the anaesthetic agent(s).

One method of testing those aspects of the hypothesis concerned with the number and size of molecular sites is to use mixtures of anaesthetics. Strict additivity should apply when anaesthetics are acting in a similar fashion at one site; significant deviations from strict additivity would support the concept of there being different sites with differing characteristics.

It is generally thought that the potencies of anaesthetics are "additive". However, many of the clinical studies on anaesthetic combinations demonstrate only that the addition of the second agent reduces the requirement of the first agent. This decrease in requirement may be either that exactly predicted from the individual potencies (i.e. strict additivity) or a greater or lesser decrease (i.e. synergism or antagonism, respectively) (fig. 1). The determination of the MAC of nitrous oxide in man using a hyperbaric chamber (Hornbein et al., 1982) has demonstrated the approximate additivity of the potency of this agent with those of other volatile agents (Eger, 1985). On the other hand, nitrous oxide and ketamine appear to have slightly antagonistic potencies: 67% nitrous oxide decreases ketamine requirements by only 40% in man (Wessels, Allen and Slogoff, 1973).

More comprehensive investigations of additivity have been carried out in animals and some indicate apparent non-additivity of anaesthetic potencies (Di Fazio et al., 1972). Studies in mice with binary mixtures of nitrous oxide, sulphur hexafluoride, argon and carbon tetrafluoride demonstrated additive behaviour in three out of five combinations and unequivocal non-additivity of sulphur hexafluoride with either argon or carbon tetrafluoride

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*Preliminary accounts of some of these data have been presented to the Anaesthetic Research Society (*Br. J. Anaesth.* (1978), 50, 1081P; *Br. J. Anaesth.* (1981), 53, 187P).

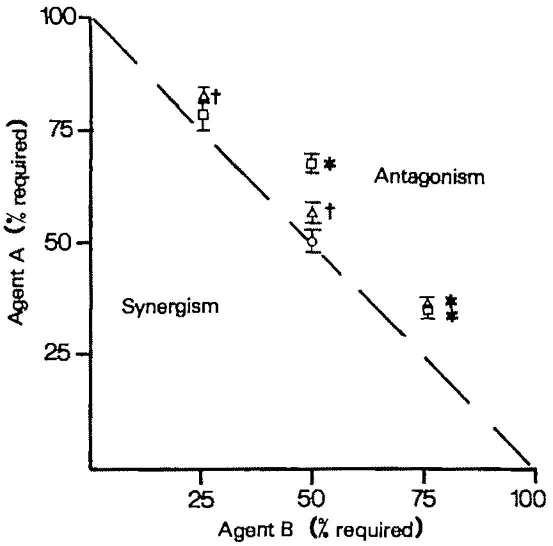

FIG. 1. The relative potencies of mixtures at ambient pressure of: methohexitone and nitrous oxide (□); Althesin and nitrous oxide (△); thiopentone and propanidid (○). The potencies of the combinations are expressed relative to those of the agents alone. The percentages refer to these relative values and not to gas volume (for example, 50% nitrous oxide mixture is 50% of its anaesthetizing concentration, that is 0.74 ATA). $^*P < 0.001$; $^\dagger P < 0.01$.

(Clarke et al., 1978). The authors of that paper surprisingly attributed the non-additivity of some of the sulphur hexafluoride mixtures to respiratory depression—an unconvincing explanation because hypoxia or hypercarbia would, if anything, be synergistic with anaesthetic potencies (Eger, 1974), not antagonistic as was observed. It may be more significant that the cases of non-additivity were revealed only at the higher pressures when sulphur hexafluoride was combined with gases of low anaesthetic potency. This is analogous to the deviations from additivity seen with some of the agents in the present study—which became much more marked at increased pressures.

The choice of anaesthetic combinations for the present study was based on the characteristics of the individual pressure reversal curves. The pressure reversal curves of some of the agents differ in their initial slopes (fig. 2), and we had ascribed this characteristic to the agents acting at different sites (Halsey, Wardley-Smith and Green, 1978). Non-additivity of different combinations of these particular agents would support the concept of separate sites. The hypothesis that the anaesthetic molecular site has a finite capacity can also be tested with mixtures of the agents. We had

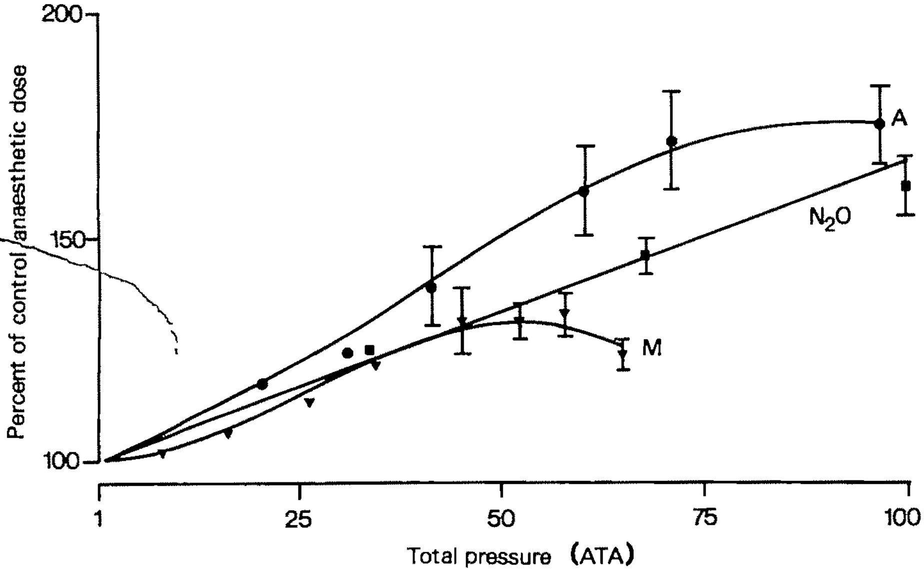

FIG. 2. Pressure reversal curves for Althesin (A), nitrous oxide (N_2O) and methohexitone (M) alone. Vertical axis: % of control anaesthetic dose at 1 ATA; horizontal axis: total pressure (ATA). Error bars ± 1 SEM. Only some error bars, but always including the largest, have been shown for clarity. Each point represents mean % of control dose for 4–10 rats.

postulated that the plateaux in some of the pressure reversal curves revealed that the capacities of the sites were limited. If this is correct, then a mixture of two agents which act at different sites should have the position of the plateau shifted to a higher pressure.

The agents selected were, first, two pairs of anaesthetics which we predicted, from the pressure reversal data for each agent alone, would be acting at different sites, one component of each appearing to act at a site with a limited capacity: (a) Althesin continuous infusion combined with the inhalation of nitrous oxide and (b) methohexitone as a continuous infusion combined with the inhalation of nitrous oxide. We also carried out control studies using two pairs of agents which we predicted were acting at the same sites: (c) thiopentone as a continuous infusion plus the inhalation of nitrous oxide, and (d) thiopentone and propanidid as continuous infusions.

MATERIALS AND METHODS

Male Sprague–Dawley rats (300–350 g) were used in all investigations. The left lateral tail vein was cannulated with a nylon cannula (o.d. 0.63 mm, Portex Ltd) which was sewn securely in place. The cannula was flushed with saline and connected to a small motorized syringe pump (Braun Perfusor) which was filled with the appropriate anaesthetic solution. A pulse signal generator was used to control the rate of infusion from outside the pressure chamber. Anaesthesia was assessed by noting the behavioural response to a 10-V, 5-ms electrical stimulus applied to the proximal 1 inch of the tail. Deep colonic temperature was maintained at 37 ± 0.5 °C and heart and respiration rates were monitored continuously. Four pairs of anaesthetics were used: (a) Althesin (alphaxalone–alphadolone acetate, Glaxo Ltd)–nitrous oxide (BOC Ltd); (b) methohexitone (Brietal, Lilly Ltd)–nitrous oxide; (c) thiopentone (Pentothal, Abbott)–nitrous oxide, and (d) thiopentone–propanidid (Epontal, Bayer Ltd). All pairs were studied as 50% mixtures; in addition, Althesin–nitrous oxide and methohexitone–nitrous oxide were studied as 25% and 75% mixtures. One component was kept constant throughout pressurization, the other being varied as required.

Before pressurization the AD_{95} for the i.v. agent was established for each animal. We defined the AD_{95} as the infusion rate at which only a small abdominal twitch occurred in response to a 10-V stimulus to the tail. The infusion rate was maintained for a minimum of 30 min to ensure that neither acute tolerance nor accumulation occurred. Additionally the waking times from this steady-state dose were determined, by switching off the anaesthetic and noting when spontaneous head movement occurred.

The animal was then placed in the pressure chamber (20 litre, maximum pressure 100 atmospheres absolute, ATA) (Bailey et al., 1977) and, for the 50% mixtures involving nitrous oxide, nitrous oxide 0.74 ATA was added. Preliminary experiments had shown the mean AD_{95} for nitrous oxide (in the absence of helium pressure) to be 1.48 ATA. The i.v. component of the mixture was decreased to 50% of its AD_{95} and its dose was subsequently adjusted, if necessary, to establish the AD_{95} exactly. In the studies with Althesin and methohexitone using 25% and 75% mixtures, 1.11 or 0.37 ATA, respectively, of nitrous oxide was added, and the i.v. agent decreased to 25% or 75% of its determined AD_{95}, and adjusted accordingly. Once a stable AD_{95} was established, additional oxygen was added to bring the Po_2 to 0.5 ATA and compression with helium (1 ATA min^{-1}) was commenced. Carbon dioxide was removed with a soda-lime scrubber. Depth of anaesthesia was estimated every 5 min and the dose of i.v. agent increased as required. Nitrous oxide was maintained at a constant partial pressure throughout compression, and its concentration verified at the end of the study with a mass spectrometer (BOC Medishield Gas Analyser).

In the case of the thiopentone–propanidid mixture, the AD_{95} values for both agents were established, and then 50% of each was infused via a Y-piece and two infusion pumps. Propanidid was kept constant throughout, whilst thiopentone was varied as required. In all other aspects the design of the study was identical to that used in the nitrous oxide mixture experiments. Where possible, compression was continued up to 100 ATA; however, in some investigations the onset of the high pressure neurological syndrome (HPNS, which includes tremors and convulsions) made this impossible. When this occurred, or at 100 ATA, the animals were humanely killed with an overdose of anaesthetic.

Analysis of data

Initially, the observed relative potency data for the agents alone and in combination at ambient pressure were plotted against each other with the straight dotted line between the potencies of the agents alone representing the case of strict additivity (fig. 1). The potency data at increased pressures were expressed as the % of control anaesthetic dose at 1 ATA for the agent which was varied, plotted against the increasing total pressure. The anaesthetic dose was increased as required, and for convenience results were analysed in terms of the mean increase of control anaesthetic dose for each 10 ATA pressure increase, that is 1–10 ATA, 11–20 ATA etc. For each mixture, a group of 6–10 rats was used. Not all rats required an increase in anaesthetic every 10 ATA—when this occurred the value for the previous 10 ATA step was taken and used to calculate the mean % increase. At the highest pressures, some rats developed tremor which made assessment of anaesthesia unreliable, and the data were excluded. Mean values were not plotted unless a minimum of four rats could be included in the value. Standard errors of the mean (SEM) were calculated for each value, and are indicated for selected points in figures 2–6; in all cases the largest SEM has been included, but intermediate SEM have been omitted for clarity. SEM was also calculated for each pressure co-ordinate, but since these were never greater than ±2 ATA, they have not been shown.

Predicted values for the increase in anaesthetic required in a mixture were calculated from data obtained for each agent alone, on the basis of simple additivity at both ambient and increased pressures. The changing influence of the component kept constant in the mixture was included. Thus:

$$\frac{P_A^M}{P_A^0}+\frac{P_B^M}{P_B^0}=1$$

where P_A^0 and P_B^0 are the anaesthetizing partial pressures (or infusion rates) of agents A and B alone at any specific pressure. P_A^M and P_B^M are the anaesthetizing partial pressures of agents A and B when used in a mixture of the two.

RESULTS AND DISCUSSION

The data for seven of the combinations at ambient pressure are illustrated in figure 1. It is clear that the combinations of nitrous oxide and methohexitone or nitrous oxide and Althesin are non-additive. In contrast, the combination of thiopentone and propanidid lies exactly on the line of strict additivity. This is in accord with the predictions of the multi-site hypothesis applied specifically to these agents. Furthermore, the rest of the data indicate non-additivity of the potencies at pressure for the agents predicted to be acting at different sites and additivity for those predicted to be acting at the same site. More interestingly, in the case of the mixtures the positions of the plateaux are shifted to higher pressures—as would be expected from the predictions based on the concept of finite capacities for the sites. However, before considering results for individual pairs of agents in detail, there are several general factors to be considered.

We were concerned initially that the assessments of the potency of the i.v. agents were based on the assumption that their clearance rates were unaffected by pressure or the presence of the other agent. Every behavioural measurement was made under steady-state conditions, but it was not technically possible to measure the corresponding plasma concentrations. With the individual agents we were also able to demonstrate that pressure did not alter the "recovery times" when the administration of the i.v. agent was discontinued, but in the investigations with mixtures the constant presence of the gaseous component precluded such a measurement. However, the assumption of non-perturbed clearance rates, in the pressure range and drug combinations chosen, is reasonable for the following reasons: (1) drug metabolism of representative types of drugs in isolated rat liver cells has been found to be unaffected by high pressure (Aanderud et al., 1979). (2) *In vivo* rat studies have demonstrated that high pressure has no appreciable effect either on the pharmacokinetics of morphine or antipyrine (Aanderud and Bakke, 1983) or on the rates of clearance of thiopentone from the brain (Aanderud, Thoner and Bakke, 1983). (3) Other studies on the sleep times of mixtures of i.v. agents administered by bolus doses at normal pressures include the demonstration of additivity of alphaxalone and alphadolone acetate, alphaxalone and propanidid, and methohexitone and propanidid (Richards and White, 1981). These data are inconsistent with any postulated change in clearance rates for mixtures of the agents. The only combination (alphaxalone and methohexitone) which was found to have synergistic sleep times had results comparable to those from equivalent *in vitro* potency studies in which there were no complications of plasma clearance (Richards and White, 1981). (4) A study of plasma concentrations of mixtures of methohexitone and

TABLE I. *Anaesthetic potencies (and standard deviations) of the agents alone at normal pressures*

Agent	Potency	*n*
Nitrous oxide	1.48 (0.076) ATA	9
Althesin	0.318 (0.078) mg kg^{-1} min^{-1}	22
Methohexitone	0.665 (0.10) mg kg^{-1} min^{-1}	20
Thiopentone	0.512 (0.099) mg kg^{-1} min^{-1}	19
Propanidid	10.1 (1.81) mg kg^{-1} min^{-1}	10

alphaxalone demonstrated directly that there were no changes in clearance rates for alphaxalone (Cooksey and Livingstone, 1983). Methohexitone did appear to have a lower rate of clearance in the presence of Althesin, but it should be noted that the doses of anaesthetics were 10 times those used in the earlier study and administered via a different route. (5) In all our cases where non-additivity was predicted, the second component of the combination was nitrous oxide—an agent which is known not to be metabolized by the same routes as the i.v. agents.

The occurrence of the HPNS at higher pressures is also a complication. Different anaesthetics affect the appearance and severity of this syndrome to differing extents (Green, Halsey and Wardley-Smith, 1977), but where the presence of tremor or convulsions led to any doubt in the assessment of anaesthetic depth, the investigation was discontinued, and any suspect results not included in the subsequent analysis. It is interesting to note that the action of the individual anaesthetics on the HPNS was not always "additive" and in some cases it was possible to continue the investigation to a higher than predicted pressure.

Finally, in this study the anaesthetic potencies have been determined in terms of the continuous infusion rate required to maintain stable anaesthesia (using AD$_{95}$ as the endpoint) and we have

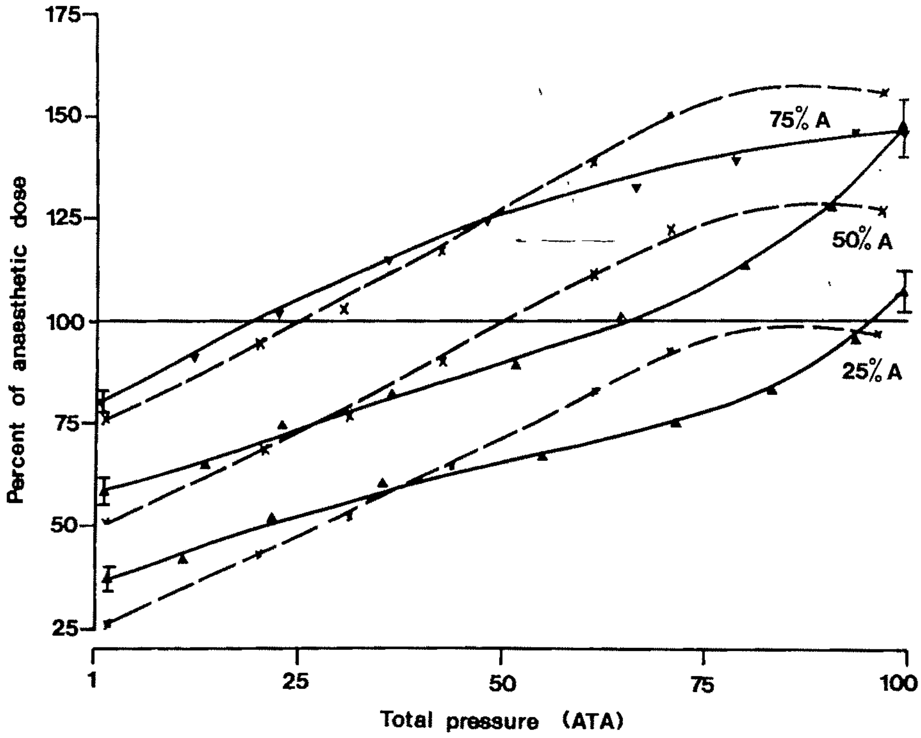

FIG. 3. The percentage of the control anaesthetic dose at 1 ATA for Althesin (A) in the presence of nitrous oxide plotted against the total environmental pressure (ATA). These data are for Althesin–nitrous oxide mixtures, nitrous oxide kept constant (75%:25%; 50%:50%; 25%:75%). Solid lines indicate the observed data. Means ± 1 SEM are indicated at the ends of each line. Intermediate SEM have been omitted for clarity, but were always within the two extremes which are shown. The dotted lines indicate the predicted data calculated on the basis of strict additivity of the potencies of the two agents at the various pressures, using the values obtained for each agent alone, shown in figure 2.

demonstrated that the dose–response curves are parallel at ambient and increased pressures (Halsey, Wardley-Smith and Green, 1978).

Nitrous oxide and Althesin

Our results for nitrous oxide in the rat (table I) agree remarkably closely with previous data obtained in mice, for example 1.47 ATA (Halsey et al., 1975), 1.50 ATA (Miller et al., 1972). Pressure reversal data for nitrous oxide in mice also compare well with the present data in the rat (fig. 2). The percentage change in the nitrous oxide ED_{50} is linearly related to the additional helium partial pressure up to 100 ATA (Halsey et al., 1975) and, in the case of nitrous oxide, it is only above this pressure that deviations in linearity have been observed (Halsey, Kent and Eger, 1976).

Results for Althesin and nitrous oxide alone are shown in figure 2 and for the mixtures in figure 3. The initial observed values for the potencies at 1 ATA are significantly different from those calculated from the agents alone. Moreover, the shapes of the pressure reversal curves are very different from those calculated on the basis of simple additivity. For example, the calculated curve for "50% Althesin with 50% nitrous oxide" (i.e. the potency of Althesin in the presence of 50% of the normobaric anaesthetizing nitrous oxide partial pressure) has an initial slope of 0.92% increase per atmosphere and has a plateau starting at approximately 80 ATA. The observed curve, however, is concave with an initial slope of 0.6% increase per atmosphere and a final slope at 90–100 ATA of 2% increase per atmosphere. This shape is consistent with previous mathematical models of the pressure reversal curves of different agents (Halsey et al., 1981). Thus the plateau for 50% Althesin–50% nitrous oxide would be predicted from the observed data to be shifted to considerably higher pressures. It has not been possible to observe this practically, because of the technical limitations of the apparatus available and because at the predicted higher pressures (in the region of 160–200 ATA) there will, in any case, be other physiological manifestations of high pressure which would invalidate the assessment of anaesthesia. However, our data to 100 ATA are not complicated by the presence of the HPNS, since both agents are effective in protecting against this syndrome.

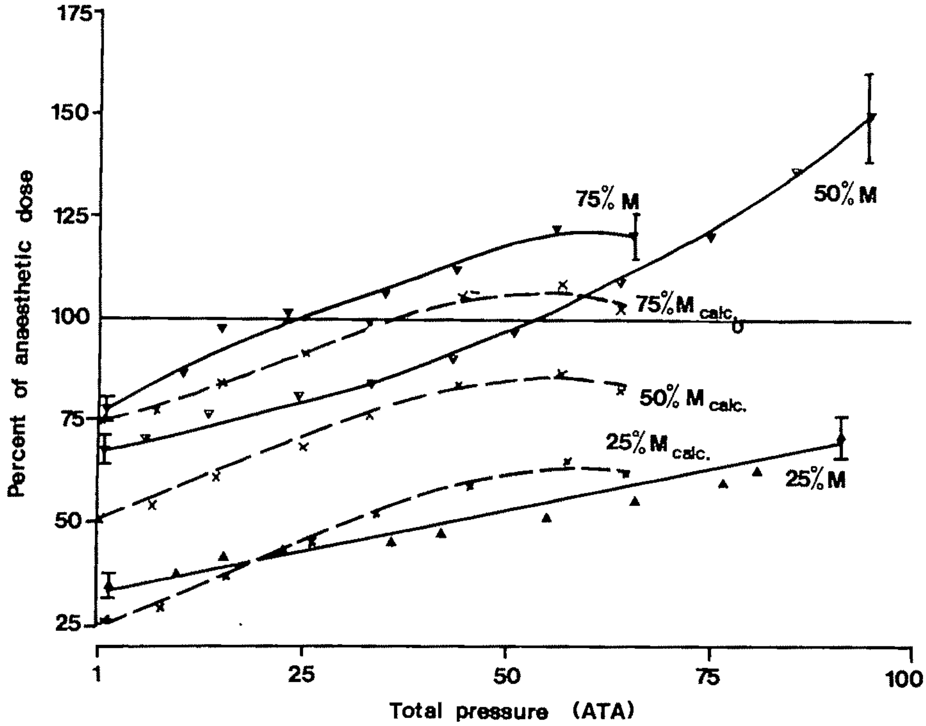

FIG. 4. The percentage of the control anaesthetic dose for methohexitone (M) in the presence of nitrous oxide. Details as for figure 3.

The contrast between the concavity of the observed pressure reversal curve and the convexity of the calculated curve is also prominent in the case of the 25% Althesin–75% nitrous oxide mixture. However, the most interesting curve in this series of mixtures is that for 75% Althesin–25% nitrous oxide. In this case there is still non-additivity at the higher pressures, but the plateau is beginning to appear at 100 ATA. Since the theoretical proportion of Althesin is three-quarters of that used alone, it was predicted that this mixture would be the one most likely to exhibit saturation of the Althesin site, albeit at a higher pressure. This was the case.

Methohexitone and nitrous oxide

Methohexitone has proved to be an unusual agent in that there is an age or weight dependency, or both, of the control anaesthetic dose (already expressed on a mg kg^{-1} basis) and of the pressure reversal data (expressed as a percentage of the control dose) (Halsey, Wardley-Smith and Green, 1982). However, once the age and weight of the animals were carefully standardized, the data were found to be reproducible (table I) and consistent with the previous work.

The initial pressure reversal slopes for methohexitone and nitrous oxide are the same (0.8% per atmosphere), but the methohexitone curve deviates from that of nitrous oxide above 48 ATA and forms a plateau (fig. 2). This plateau has only been characterized up to 66 ATA because of the interactions with the high pressure neurological syndrome. At higher pressures convulsions occurred and, where these were continuous or severe, it was impossible to differentiate objectively between unconsciousness associated with the post-convulsive phase and that resulting from anaesthesia.

The position of the methohexitone plateau and the deviations of the two curves led to the hypothesis that the two agents acted at different sites with different capacities. The normobaric potencies of the mixtures indicate a degree of antagonism, especially in the 50:50 mixture (fig. 1).

The pressure reversal data of the mixtures (fig. 4) were consistent with the hypothesis that the two

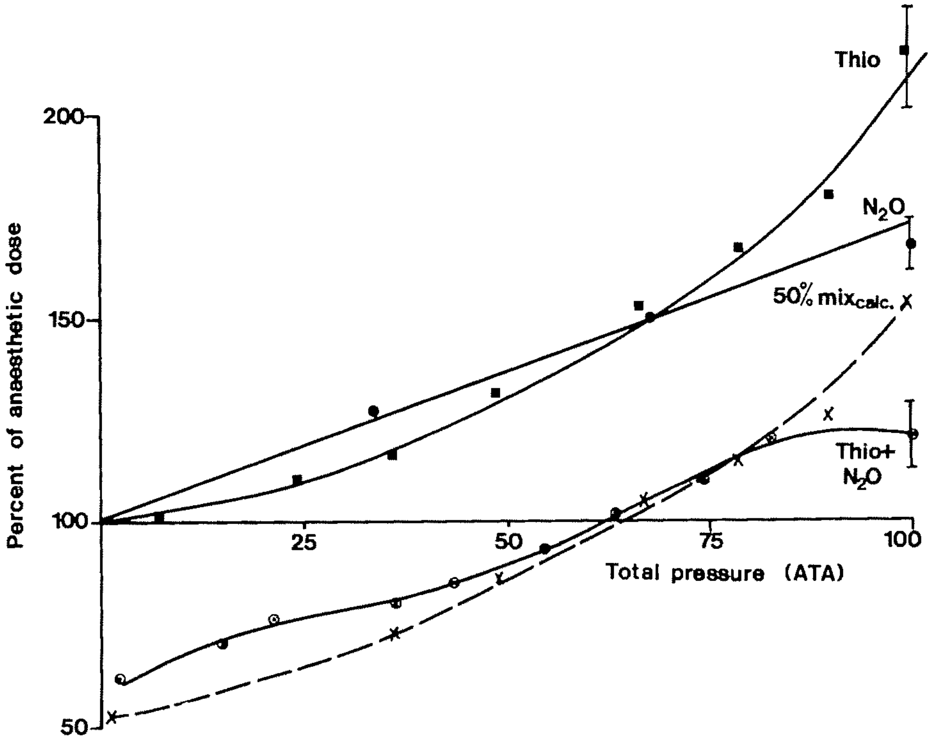

FIG. 5. Pressure reversal data for thiopentone and nitrous oxide, separately and as 50% mixture. Axes and error bars as in figure 3. Dotted line represents calculated values for 50% mixture based on simple additivity.

agents acted at different sites, in that there was antagonism relative to the predicted potencies at pressure. There was no evidence of any plateau in the 25 % or 50 % methohexitone mixtures, but the plateau was present in the 75 % mixture. This concentration dependence is exactly what was predicted from the concept of a finite capacity for the methohexitone site.

Finally, it will be noted that the 50:50 mixture was studied at higher pressures than the other mixtures or methohexitone alone. This was because there were no interfering signs or symptoms of the high pressure neurological syndrome. A possible explanation is that the mixture of methohexitone and nitrous oxide behaves more like nitrous oxide in its protective effects on the HPNS. The pressures at which tremors and convulsions occur with or without anaesthetics in this strain of rat have already been established (Green, Halsey and Wardley-Smith, 1977). It is not possible to make any calculations for the mixture because the convulsion threshold pressure in the presence of nitrous oxide is greater than 100 ATA. However, the 25 % and 50 % methohexitone mixtures have increased the convulsion pressure from 50–60 (as observed with methohexitone alone for this weight range of rats) past 76 ATA (as in the unanaesthetized control observations).

Thiopentone and nitrous oxide

Results are shown in figure 5. Thiopentone up to 75 ATA had the same pressure reversal characteristics as nitrous oxide. If the data above this pressure are included, the relationship between potency and pressure is no longer linear, and approximates best to the equation:

$$y = \frac{P}{2.52-0.0175\,P}$$

where y is the potency and P is the pressure.

At pressures less than 100 ATA the slope of the thiopentone curve fitting this equation increased steadily with pressure (Halsey et al., 1981). This appeared to be contrary to the concept of a finite capacity for the anaesthetic site. Alternative explanations included a change in the slope of the dose–response curve at pressure or an increase in the rate of metabolism of the agent. The more probable reason for the increasing slope is that,

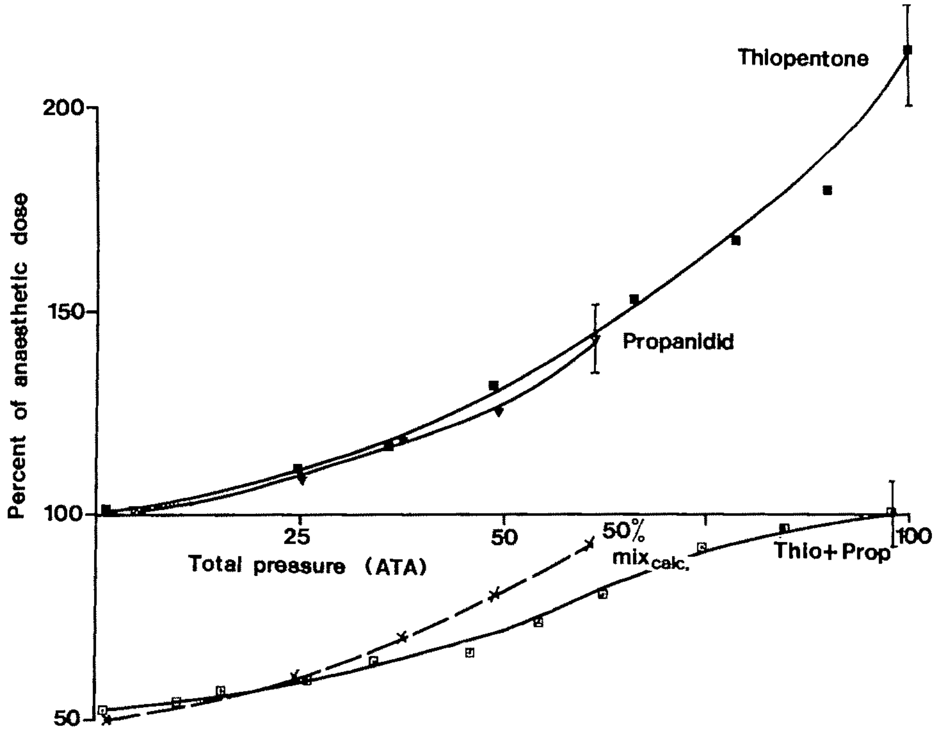

FIG. 6. Pressure reversal data for thiopentone and propanidid, separately and as 50 % mixture. Axes, error bars and calculated line as for figure 5.

above 75 ATA, there is a change in the physical characteristics of the thiopentone site, resulting in an increased compressibility. This is what would be predicted *a priori* if the anaesthetic was interacting with the lipid bilayer rather than with a neuronal protein in the membrane.

The postulate that thiopentone and nitrous oxide were acting at the same site can only apply at pressures below 75 ATA—before the two curves deviate. Under such conditions the mixture of the two agents is additive as predicted. The behaviour of the mixture above 75 ATA cannot be explained at the moment.

Thiopentone and propanidid

We predicted that these anaesthetics shared a common site of action because they had identical pressure reversal curves (fig. 6). The data for propanidid alone could only be obtained up to 61 ATA because of the complicating effects of the HPNS. The mixture of the two agents indicated complete additivity, exactly in accord with the prediction (fig. 6).

The observations with the mixture could be continued up to 95 ATA because HPNS appeared to be ameliorated under these conditions. This is surprising because the convulsion threshold pressures for thiopentone and propanidid are 83 and 52 ATA, respectively, compared with a control convulsion threshold pressure of 76 ATA (Green, Halsey and Wardley-Smith, 1977). However, the mixture actually protects against high pressure convulsions despite one of the individual components exacerbating the syndrome.

CONCLUSION

The results obtained with the mixtures of the agents indicate non-additivity of anaesthetic potencies of those agents predicted to be acting at different sites and additivity with those agents predicted to be acting at the same site. The initial slopes of the pressure reversal curves for the mixtures are consistent with those predicted from the agents alone. The positions of the plateaux (where they occur) are shifted to higher pressures in the mixtures. Such shifts are dependent on the composition of the mixture, as expected from the predictions based on the concept of a finite capacity of the site. The overall results are, thus, in accord with the predictions of the multi-site hypothesis.

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END-TIDAL CARBON DIOXIDE CONCENTRATION AS AN INDICATOR OF PULMONARY BLOOD FLOW DURING CLOSED HEART SURGERY IN CHILDREN

A Report of Two Cases

J. L. SCHULLER, J. G. BOVILL AND A. NIJVELD

In patients with restricted pulmonary blood flow, manipulation of the lung, pulmonary artery (PA) or ductus arteriosus (PDA) can decrease the pulmonary blood flow further and result in a critical reduction in arterial oxygenation, bradycardia and systemic arterial hypotension. Since there is often a delay between the alteration in pulmonary blood flow and the appearance of changes in systemic haemodynamics, a situation can develop in which pharmacological intervention may be ineffective. Early recognition is, therefore, vital so that pulmonary blood flow can be restored immediately.

Since a marked decrease in pulmonary blood flow will also result in a decrease in carbon dioxide elimination from the lung we monitor the end-tidal carbon dioxide concentration (E'_{CO_2}) continuously in such patients. Our experience suggests that after manoeuvres which reduce pulmonary blood flow, a decrease in E'_{CO_2} is detectable within a few respirations, whereas bradycardia and systemic hypotension may not develop for several minutes. This is illustrated by two case reports.

SUMMARY

The value of the continuous monitoring of end-tidal carbon dioxide concentration as an indicator of the acute intraoperative interruption of pulmonary blood flow, in patients with pre-existing restrictions of pulmonary blood flow undergoing closed heart surgery, is illustrated by two case reports. Decreases in end-tidal carbon dioxide concentration often appeared several minutes before the changes in systemic haemodynamics.

CASE REPORTS

Patient 1

A 2-day-old boy, weighing 3.2 kg, with pulmonary atresia and an intact ventricular septum was scheduled for the creation of a shunt from the left subclavian artery to the mainstem of the PA. Prostaglandin E_1 0.04 μg kg^{-1} min^{-1} was infused to maintain the patency of the ductus arteriosus. No premedication was given. Anaesthesia was induced with ketamine 8 mg i.v. followed by suxamethonium 3 mg i.v., and the trachea was intubated with a 3.5-mm uncuffed tube. Halothane 0.4% in oxygen, supplemented by fentanyl 10 μg was used to maintain anaesthesia. Muscle relaxation was produced by pancuronium 0.3 mg and the lungs were ventilated by a Siemens Servo ventilator. The inspired minute volume was set at 2.5 litre min^{-1} and E'_{CO_2} was measured (Siemens CO_2 Analyzer 930). Arterial pressure was measured via a catheter in the left femoral artery.

Blood-gas analysis, after skin incision, showed [H$^+$] 36.3 nmol litre^{-1}, Pa_{CO_2} 3.9 kPa, Pa_{O_2} 6.9 kPa and BE −2.8 mmol litre^{-1}. E'_{CO_2} was 2.3%. The mainstem of the PA was occluded using a vascular snare. Within 15–20 s the E'_{CO_2} decreased from 2.3 to 0.9% and after a delay of 1 min the heart rate decreased from 143 to 80 beat min^{-1} and the arterial pressure from 60/40 to 30/20 mm Hg. The snare was loosened. Blood-gas analysis at this time revealed [H$^+$] 64.6 nmol litre^{-1}, Pa_{CO_2}

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6.0 kPa, Pa_{O_2} 8.5 kPa and BE -11.8 mmol litre^{-1}. Sodium bicarbonate 15 mmol was given in divided doses. The snare was tightened and once again the E'_{CO_2} decreased from 2.3 to 1.0%, to be followed, after a delay, by bradycardia and hypotension.

The prostaglandin E_1 infusion was increased to 0.08 μg kg^{-1} min^{-1} and isoprenaline 4 μg kg^{-1} min^{-1} was given, but did not improve the situation. The shunt was connected to the mainstem of the PA and completed in 24 min. Heart rate had decreased to 30 beat min^{-1} and arterial pressure was 20/10 mm Hg, despite increasing the dose of isoprenaline. Blood-gas analysis showed [H^+] 38.9 nmol litre^{-1}, Pa_{CO_2} 2.1 kPa, Pa_{O_2} 5.6 kPa and BE -3.6 mmol litre^{-1}.

The child died 25 min later. In retrospect, tightening of the snare must have obstructed the ductus arteriosus.

Patient 2

A 2-month-old girl, weighing 3.2 kg, with a univentricular heart, pulmonary atresia and a PDA was scheduled for a modified Blalock–Taussig shunt. Prostaglandin E_1 0.04 μg kg^{-1} min^{-1} was given i.v. No premedication was given. Anaesthesia was induced with ketamine 8 mg i.v. followed by suxamethonium 3 mg i.v., and the trachea was intubated with a 3.5-mm uncuffed tube. Halothane 0.5% in oxygen, supplemented with fentanyl 15 μg, was used to maintain anaesthesia. Muscle relaxation was produced by pancuronium 0.3 mg and the lungs were ventilated with a Siemens Servo ventilator. The inspired minute volume was set at 3.0 litre min^{-1} and E'_{CO_2} was monitored with a Siemens CO_2 Analyzer 930.

Arterial pressure was measured via a catheter in the right radial artery. Blood-gas analysis after skin incision, but before manipulation of the lung, showed [H^+] 45.7 nmol litre^{-1}, Pa_{CO_2} 5.3 kPa, Pa_{O_2} 5.7 kPa and BE -3.4 mmol litre^{-1}. During surgery the ductus was found to be connected to a very narrow left PA. A modified Blalock–Taussig shunt was placed on the left PA distal to the ductus arteriosus. In order to asses the importance of flow to the right lung, the left PA was clamped between the bifurcation and the ductus arteriosus. This resulted in a decrease in E'_{CO_2} from 3.2 to 1.8%. The clamp was repositioned and this produced a similar response (fig. 1). The clamp was repositioned again and E'_{CO_2} decreased to only 2.4% and remained at that value. Six minutes later, blood–gas analysis showed [H^+] 50.1 nmol litre^{-1}, Pa_{CO_2} 5.6 kPa, Pa_{O_2} 6.3 kPa and BE -4.8 mmol litre^{-1}.

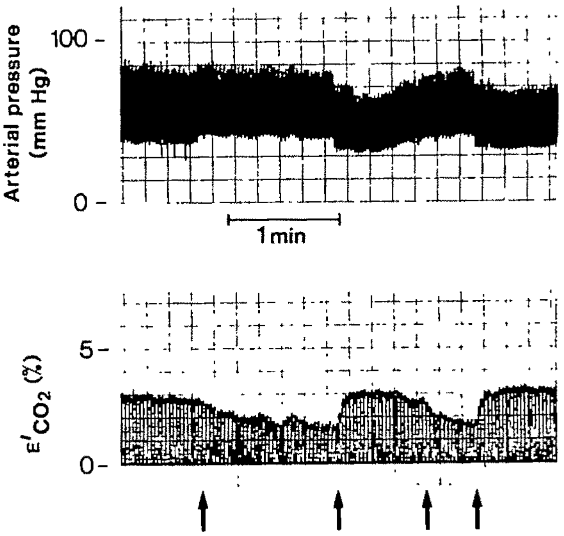

FIG. 1. Changes in E'_{CO_2} and arterial pressure in patient 2. At the first arrow a stenotic area in the left pulmonary artery between the origin of the ductus arteriosus and the bifurcation was clamped. The clamp was removed at the second arrow. The sequence was repeated again at the third and fourth arrows.

It was decided to place a patch over the stenotic area in the left PA between the bifurcation and the ductus arteriosus. When this section was clamped, E'_{CO_2} decreased from 3.2% to 2.4% without any alteration in haemodynamic variables. Sodium bicarbonate 10 mmol was given in divided doses. After 40 min of clamping, heart rate, which had been stable at 156 beat min^{-1}, decreased rapidly to 112 beat min^{-1}. Blood–gas analysis showed [H^+] 58.9 nmol litre^{-1}, Pa_{CO_2} 7.6 kPa, Pa_{O_2} 2.1 kPa and BE -3.6 mmol litre^{-1}. The clamp was removed and calcium laevulinate 0.5 mmol given. Haemodynamic variables returned immediately to their previous values. Blood-gas analysis 15 min later showed [H^+] 40.7 nmol litre^{-1}, Pa_{CO_2} 5.2 kPa, Pa_{O_2} 6.3 kPa, and Be -0.5 mmol litre^{-1}. At the end of surgery neuromuscular blockade was antagonized with atropine 0.1 mg and neostigmine 0.3 mg. The child awakened immediately and the trachea was extubated. Further recovery was uneventful.

DISCUSSION

Heneghan, Scallan and Branthwaite (1981) found that monitoring E'_{CO_2} was unreliable in infants with restricted pulmonary blood flow because of the magnitude of the blood–end tidal carbon dioxide gradient. We agree that E'_{CO_2} is not a reliable indicator of Pa_{CO_2} and, therefore, of the adequacy of ventilation in these children. However, E'_{CO_2} also reflects pulmonary perfusion. If ventilation is held constant, changes in pulmonary perfusion may be reflected in the E'_{CO_2} (Robinson, 1983). Therefore, recording the E'_{CO_2} can be particularly valuable in patients with restricted pulmonary blood flow undergoing an operative procedure which involves manipulation of the PA.

In our experience (patient 1), a decrease in E'_{CO_2} often occurs 1–3 min before there is evidence of bradycardia or arterial hypotension when pulmonary blood flow is restricted acutely. The state of oxygenation and the magnitude of the reduction in pulmonary blood flow may be of importance in determining the interval between a decrease in E'_{CO_2} and the occurrence of bradycardia and hypotension.

Before clamping a PA one should be confident that the contralateral lung is adequately ventilated, that any acidosis is corrected and that there is an optimal arterial pressure. During the period of clamping, the lungs should be ventilated with 100% oxygen. In the neonate, the use of prostaglandin E_1 may be beneficial in maintaining ductal blood flow. If, despite these measures, a significant decrease in E'_{CO_2} occurs when a PA is occluded, the possibility of traction on the mainstem of the PA or on the ductus should be considered and corrected (as in patient 2). If occlusion remains poorly tolerated, consideration should be given to an alternative operative procedure. In retrospect, this policy should have been followed in patient 1. Surgical manipulation can cause a further reduction in pulmonary blood flow and a decrease in E'_{CO_2}. When this occurs the surgeon should immediately be warned, since the persistence of this situation may cause hypoxia and possibly irreversible bradycardia and hypotension.

In those patients who developed a significant decrease in E'_{CO_2} after clamping, or who have pre-existing hypoxia, arterial blood-gas analysis should be performed at frequent intervals during the period of clamping. It is imperative to correct any acidosis adequately since this can cause an increase in pulmonary vascular resistance and a further decrease in pulmonary blood flow.

In conclusion, the continuous monitoring of E'_{CO_2} during operations where the pulmonary blood flow may be partially interrupted, can give valuable information. In this situation a decrease in E'_{CO_2} often occurs several minutes before changes in systemic haemodynamics.

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ANAESTHETIC PROBLEMS ASSOCIATED WITH WEAVER'S SYNDROME

D. R. TURNER AND J. W. DOWNING

A child with the clinical features of Weaver's Syndrome presented for surgery twice within a period of 6 weeks. Weaver's Syndrome is a very rare condition characterized by accelerated growth beginning prenatally, advanced osseous maturation, unusual craniofacial appearance, herniae and camptodactyly.

SUMMARY

A child of 14 months with the clinical features of Weaver's Syndrome presented for surgery twice within a period of 6 weeks. The prime anaesthetic difficulty associated with this case, namely a difficult airway, and other problems related to Weaver's syndrome, are discussed.

CASE REPORT

A 14-month-old male child weighing 34 kg, with accelerated skeletal growth and the abnormal facies of 'Weaver's Syndrome' (fig. 1), was admitted to the King Edward VIII Hospital, Durban for investigation. He was found subsequently to have an incarcerated left inguinal hernia and was scheduled for an emergency laparotomy. Pre-operative assessment of the child highlighted a number of potential problems. The child's head was the size of an adult (57 cm in circumference) (fig. 2), but the jaw was small and the chin receding (fig. 3). The larynx lay anterior and cephalad. The child's mouth was of normal size for his head, but his teeth were underdeveloped and his tongue was large and thickened. The child's neck was short and broad. Consequently his ability to extend his neck was limited. He had a marked kyphosis with an angle of flexion of 65°. He had excessive amounts of very mobile subcutaneous fat, both around his neck and on his limbs. No veins could be seen or palpated.

Fortunately, the hernia was reduced manually before the child received his premedication, and it was decided to postpone surgery and repair the hernia as an elective procedure.

Next day, the child received ketamine 2 mg kg^{-1}

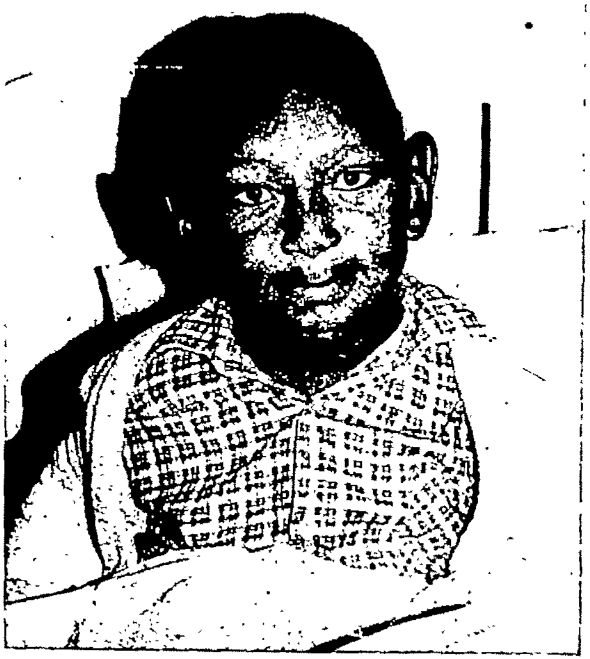

FIG. 1. Frontal view of 14-month-old child with Weaver's Syndrome. Note large size of head and unusual facies.

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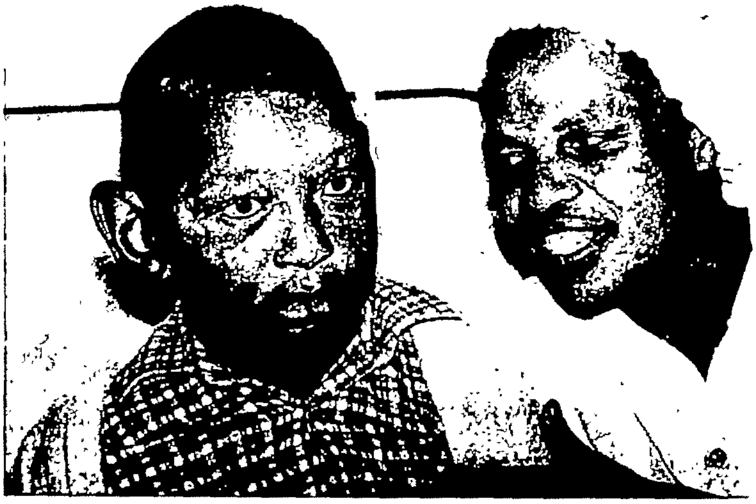

FIG. 2. Fourteen-month-old boy manifesting Weaver's Syndrome with his mother. Note adult head size and abnormal facies. He also was markedly kyphotic (65° angle).

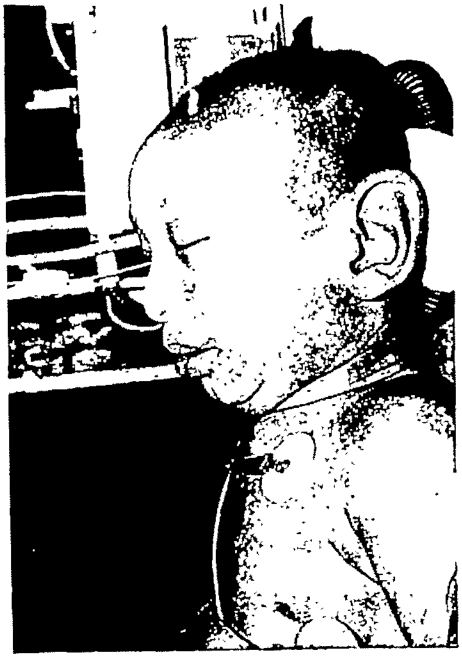

FIG. 3. Lateral view of 14-month-old boy with Weaver's Syndrome. Note large head, short neck and relatively under-developed mandible which made intubation difficult.

i.m. in theatre to facilitate a gaseous induction of anaesthesia. This produced sufficient sedation to allow the insertion of an i.v. cannula. After gaseous induction with halothane and nitrous oxide in oxygen, direct laryngoscopy was performed using a large MacIntosh blade. The epiglottis could not be seen and visualization of either vocal cords or laryngeal inlet was impossible. Anaesthesia was continued with a Guedel airway (No. 3) and a mask (No. 3) without difficulty. The airway was easy to maintain and the child breathed nitrous oxide, oxygen and halothane spontaneously via a Magill (Mapleson A) system. The patient made an uneventful recovery.

He presented a second time, 6 weeks later for repair of a substantial umbilical hernia. Premedication was with diazepam syrup orally 2 h before operation, but this proved inadequate and ketamine 2 mg kg^{-1} i.m. was given.

The same anaesthetic technique was used for this procedure as for the previous operation on the inguinal hernia and the child's airway was never compromised. A further attempt was made to visualize the vocal cords, but only the tip of his rigid V-shaped epiglottis could be seen.

DISCUSSION

Weaver's Syndrome is a rare overgrowth syndrome beginning prenatally with accelerated skeletal maturation, unusual facies and camptodactyly. First described by Weaver and colleagues (1974) there have been a number of reported cases since (Moreno et al., 1974; Gemme et al., 1980; Majewski et al., 1981; Weisswichert, Knapp and Willich, 1981), but the patient described has the grossest features of any of the previous cases presented in the literature. Of the seven cases reported by the above authors and ourselves, six had herniae—either inguinal or umbilical and in some cases, both. There is a significant risk, therefore, of small bowel obstruction in these children and, therefore, a need to protect the airway from aspiration during emergency surgery.

We were fortunate in this child not to require tracheal intubation to protect the airway. Obviously, had emergency surgery been undertaken such a need would have arisen, to prevent the aspiration of stomach contents.

It is worthy of note that the child first presented for anaesthesia at the age of 1 month, when a general anaesthetic was given for a scan of his enlarged head. At that time the anaesthetist had great difficulty in locating the larynx, but ultimately succeeded in passing a size 4 mm uncuffed oral tube through an apparently normal larynx. At that age, the patient's head was smaller and presumably the laryngeal anatomy not as distorted as on the later occasions described here.

White and Kander (1975) suggested that the most important factor determining the ease of direct laryngoscopy was the posterior depth of the mandible. When large, this was thought to hinder displacement of soft tissues. Other important measurements reported were: an increase in the anterior depth of the mandible and a decrease in the distance from the occiput and the spinal process of C1. Cass, James and Lines (1956) considered the most important factors to be: short muscular neck and a full set of teeth; receding lower jaw; protruding upper incisors and poor mobility of the tempero–mandibular joint. However, a recent study by Van der Linde, Roelofse and Steenkamp (1983) compared eight jaw measurements and five spinal measurements from 13 patients in whom difficulty had been experienced during direct laryngoscopy, with the same measurements in 13 control patients. They used xerographic radiographs for their measurements and could find no statistical difference between the two groups. They concluded that no single factor determined the ease of direct laryngoscopy, but that a combination was important.

Our patient had a series of skull radiographs performed to assess his anatomy, as he is now being considered for spinal surgical correction of his gibbus before this defect causes any neurological damage. As this child had poorly developed teeth and full jaw movement, these factors presented no problems. However, his bull neck and receding lower jaw caused difficulties because of the position of his larynx.

A number of methods have been described to facilitate tracheal intubation in difficult patients. Awake intubation (Duncan, 1977), with either local anaesthetic spray or a superior laryngeal nerve block, is a well documented and safe method of managing patients with abnormal laryngeal anatomy, but only applicable to patients who are co-operative, which was not the case with the patient presented here.

The technique of blind nasal intubation in the anaesthetized patient as advocated by Defalque (1971) could have been utilized, but it was considered that this would have subjected the child to unnecessary naso–laryngeal trauma in a patient in whom a tracheal tube was not essential.

Bearman (1962) described the use of a hook, and Waters (1963) suggested that a catheter passed through the cricothyroid membrane could be used as a guide for the tracheal tube. Murphy (1967) supported the use of a fibreoptic endoscope and Taylor and Towey (1972) a fibreoptic bronchoscope as aids to intubation. While the fibreoptic equipment is helpful in expert hands, it is not a suitable alternative for an anaesthetist with little or no prior experience in its use. One is also limited by the size of the scope, which prevents the use of the smaller tracheal tubes. Cricothyroid puncture may well have aided intubation, but perhaps the least invasive method of protecting the child's airway would have been to have used an oesophageal obturator as described by Don Michael, Lambert and Mehran (1974) and Merrifield and King (1981).

Weaver's Syndrome presents a challenge to the anaesthetist, especially when the clinical manifestations are as pronounced as they were in the reported case. The major problem appears to be the position of the larynx which, although normal for a child of 14 months, was inappropriately placed for his adult-sized head. Should he present again for corrective surgery of his gibbus, intubation may be effected by the blind nasal route or with a fibreoptic device, once the dimensions of the laryngeal inlet have been determined. These could perhaps be ascertained using computerized axial tomography.

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Photographs of the child are reproduced with the permission of his mother, International News and Features, Muldersdrift and Rex Features Ltd, London.

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Br. J. Anaesth. (1985), 57, 1264–1269

CORRESPONDENCE

ETOMIDATE AND ADRENOCORTICAL SYNTHESIS IN MAN

Sir,—We read with interest the report on the effects of a bolus dose of etomidate on cortisol and ACTH secretion (Duthie, Fraser and Nimmo, 1985). We cannot, however, accept the conclusion that "a bolus dose of etomidate 0.3 mg kg^{-1} causes no significant adrenocortical suppression".

Other studies have noted an increase in cortisol secretion which occurs about 1 h after the induction of anaesthesia with thiopentone (Fragen, Shanks and Molteni, 1983; Yeoman et al., 1984; Moore et al., 1985) which was not seen in comparative groups given etomidate for induction. The two studies in patients undergoing "minor" surgical procedures (diagnostic laparoscopy—Fragen, Shanks and Molteni; inguinal hernia repair—Yeoman and others) indicated that the cortisol response in the thiopentone groups was decreasing at 3 h after induction. As blood sampling was not performed by Duthie, Fraser and Nimmo between 1 and 4 h after induction, it is hardly suprising that a cortisol stress response was not seen. The prolonged cortisol response reported by Moore and colleagues in patients undergoing abdominal hysterectomy was probably related to the longer duration of surgery and the greater surgical "stress".

In conclusion, we feel that the authors are not justified in their assertion that boluses of etomidate do not cause significant adrenocortical suppression, because they did not sample during the time that a cortisol response would be expected.

A. J. Byrne
P. M. Yeoman
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Sir,—I read with interest the paper by Duthie, Fraser and Nimmo (1985). The authors failed to demonstrate significant differences in cortisol, corticosterone or ACTH concentrations when either etomidate or thiopentone was given to induce anaesthesia. They also suggest that the incomplete inhibition of cortisol synthesis was probably compensated for by an increase in ACTH secretion. They did not find a significant increase in ACTH, but it is true that there is a marked variability in ACTH concentrations. However, if their hypothesis is correct (that ACTH compensates for partial inhibition of cortisol synthesis) should not they demonstrate a significant decrease in cortisol concentrations first, since one would expect plasma cortisol concentration to decrease first and then the ACTH concentrations to increase (feed back mechanism)?

Their results, however (no significant difference in cortisol concentrations between etomidate and thiopentone patients), can be explained easily on the basis that their patients had minor or surface surgery.

We do know that etomidate inhibits steroid synthesis (Fry and Griffiths, 1984), but we also know that the type of surgery influences markedly plasma cortisol concentrations (Clarke, Jonhston and Sheridan, 1970). So in some operations, like laparotomy, cortisol is expected to increase as a response to surgical stress. This increase will not occur after etomidate as the drug inhibits the adrenal cortex at the enzyme level. Indeed, Fragen and colleagues (1984) noted, in patients submitted to gynaecological laparotomy, that plasma concentrations of cortisol and aldosterone 1 and 2 h after induction were significantly lower with etomidate than with thiopentone. In contrast, Wagner and White (1984) studied patients who had minor surgery (cervical biopsy) and found similar cortisol and aldosterone concentrations before, during and after operation with either thiopentone or etomidate, but the adrenocortical response to exogenous ACTH stimulation was blunted in the patients receiving etomidate.

Owen and Spence (1984) point out that further similar clinical studies will offer no more than reconfirmation that etomidate suppresses the adrenal cortex.

It appears that the type of surgery accounts for the significant or not significant differences in cortisol concentrations between the etomidate and thiopentone groups reported in the above mentioned studies and not a different degree of inhibition of adrenal cortex by an i.v. bolus injection of etomidate. So an i.v. bolus injection of etomidate produces a "silent" inhibition of the adrenal cortex, but it significantly prevents the response of the adrenal cortex to an "increased stress" such as that caused by major surgery.

A. Fassoulaki
Athens

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Wagner, R. L., and White, P. F., (1984). Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology*, 61, 647.

Sir,—The recent paper by Duthie, Fraser and Nimmo (1985) suggests that the induction of anaesthesia with a single bolus dose of etomidate 0.3 mg kg^{-1} is not associated with significant depression in cortisol concentration. In support, they cite the data of Sebel, Verghese and Makin (1983); while quoting our data (Sear et al., 1983) to show an effect when the drug is given by continuous infusion for the maintenance of anaesthesia. A re-examination of our data reported elsewhere in three separate studies (Sear et al., 1983; Moore et al., 1985; Sear, Atherden and Edwards, 1985) does not support their argument.

Thirty-five premenopausal women undergoing abdominal hysterectomy were studied. All were premedicated with diazepam 10 mg by mouth 2 h before operation. Anaesthesia was induced in all patients between 08.00 and 10.00 h. Patients were randomly allocated, within the separate studies, to receive one of three anaesthetics:

Thiopentone group: Thiopentone 4 mg kg^{-1} for induction of anaesthesia, and maintenance with 67% nitrous oxide in oxygen supplemented with 0.5% halothane ($n = 14$).

Etomidate bolus group: etomidate 0.3 mg kg^{-1} for induction, and maintenance as in the previous group ($n = 10$).

Etomidate infusion group: etomidate 0.3 mg kg^{-1} for induction, and maintenance with an infusion of etomidate 10 μg kg^{-1} min^{-1} to supplement 67% nitrous oxide in oxygen ($n = 11$).

All patients received alcuronium 0.25 mg kg^{-1} to produce neuromuscular blockade, and fentanyl 3 μg kg^{-1} for additional analgesia. Blood samples were taken before induction, at the end of surgery, and 4 h after induction; cortisol and glucose concentrations were measured in all patients, and aldosterone concentration in 25 patients. Blood-glucose concentration was measured, as the magnitude of the increase during surgery has been equated with the severity of the surgical trauma (Hall, 1985).

Table I shows blood-glucose concentrations and serum cortisol and aldosterone concentrations in the three groups of patients. There were no significant differences in the glycaemic response between the patients. There were, however, significant differences in the cortisol responses between the groups. At the end of surgery, and at 4 h after induction, the cortisol concentrations in the thiopentone group were significantly greater than in either of the other two groups ($P < 0.001$). There were no differences in cortisol concentrations between the two groups receiving etomidate, perhaps indicating that, if the drug does have a dose–response relationship on cortisol suppression, both doses in this study were probably acting maximally.

On the other hand, the three groups showed a difference in response when the effect on aldosterone secretion was studied. In the thiopentone group, a significant increase occurred both at the end of surgery and at 4 h while in the etomidate groups there was a dose-related inhibition of aldosterone secretion. In the bolus group, there was no increase in hormone concentrations at the end of surgery, but a significant increase by 4 h ($P < 0.05$). In the infusion group, aldosterone concentrations decreased by the end of surgery ($P < 0.01$), and were still lower than the preinduction value by 4 h. We also observed a differential effect on aldosterone percursor

TABLE I. *Blood-glucose and serum cortisol and aldosterone concentrations (mean ± SD) before induction (sample 1), at the end of surgery (sample 2), and 4 h after induction (sample 3) in patients receiving either thiopentone or etomidate for induction, or etomidate for induction and maintenance of anaesthesia. The duration of surgery was comparable in the three groups. Data compared between groups by the Mann–Whitney* U *test. Data within groups compared with the preinduction value by the Wilcoxon matched pairs signed ranks test* († $P < 0.05$; * $P < 0.01$)

	Glucose (mmol $litre^{-1}$)			Cortisol (nmol $litre^{-1}$)			Aldosterone (pmol $litre^{-1}$)		
	1	2	3	1	2	3	1	2	3
Thiopentone (TP)	4.89 (0.57)	6.39 (1.08)*	7.26 (1.62)*	323 (110)*	878 (241)*	1042 (236)*	271 (219)	777 (171)*	714 (225)*
Etomidate (bolus) (EB)	4.70 (0.58)	6.01 (1.02)*	6.21 (1.19)*	381 (124)	251 (52)*	316 (112)	253 (49)	276 (126)	321 (106)†
Etomidate (infusion) (EI)	5.01 (0.49)	7.05 (0.74)*	8.13 (3.21)*	359 (142)	264 (115)*	294 (96)	131 (73)	74 (64)*	105 (41)
Significance between groups	—	—	—	—	TP *v*. EB and EI: $P < 0.001$	TP *v*. EB and EI: $P < 0.001$	—	TP *v*.EB and EI: $P < 0.001$ EB *v*. EI: $P < 0.002$	TP *v*. EB, TP *v*. EI, EI *v*. EB: all $P < 0.001$

synthesis, 11 deoxycorticosterone concentration being increased in both groups receiving etomidate, but significantly higher in those receiving the single bolus dose (Sear, Atherden and Edwards, 1985). As our previous study showed an effect of infusions of etomidate on 11β-hydroxylation (Moore et al., 1985), this effect on 11 deoxycorticosterone indicated a second, and probably dose-related, inhibition on early pathway synthesis (for example cholesterol side-chain cleavage).

Why are our results different from those of Duthie and colleagues? It may relate to the magnitude of the surgical stress, a uniform induction time avoiding diurnal variations in hormone concentrations, or a sex difference (all Duthie's patients being male). In our studies, 15 of the patients receiving etomidate had cortisol concentrations at the end of surgery below the normal laboratory limits of 280–690 nmol litre^{-1}. Although our previous study (Moore et al., 1985) showed a significant and comparable increase in ACTH concentration in patients receiving either thiopentone or etomidate by infusion, the results presented here do not agree with the view of Duthie and colleagues that the effect of a bolus dose of etomidate is to cause partial inhibition of the 11β-hydroxlase enzyme without significant adrenocortical suppression.

J. SEAR
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Sir,—Thank you for allowing us the opportunity to reply to the letters of Drs Fassoulaki, Sear, and Byrne and Yeoman.

The response of cortisol to adrenocorticotrophic hormone (ACTH) is rapid and concentrations of the two hormones quickly attain equilibrum. Therefore, differential changes in concentration of the type suggested by Dr Fassoulaki would not have been apparent in the sampling regimen we used. Also, our regimen would not detect changes occurring only at 3 h after induction of anaesthesia.

It is difficult to make a quantitative comparison of the surgical "stress" imposed on our patients and those of Dr Sear, since plasma ACTH concentrations were variable in ours and not reported in theirs. However, the much higher plasma cortisol concentrations after surgery reported by Dr Sear suggest that the differences between the reports may be explained by differences in surgical "stress".

The locus of action of etomidate is not in dispute. We presented unequivocal evidence of an inhibition of 11β-hydroxylase activity and allude in our discussion to other studies which suggest that etomidate may have additional effects earlier in the steroid biosynthetic pathway. These effects would not have been apparent from the assays we performed, but have been detailed elsewhere (Vanden Bossche et al., 1984).

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R. FRASER
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INTRATHECAL MORPHINE AND MULTIPLE FRACTURED RIBS

Sir,—Intrathecal morphine has been used extensively to provide pain relief both in the postoperative period, and in patients with cancer. It has not, however, to date been used in the treatment of thoracic injuries.

This case report illustrates the satisfactory use of intrathecal morphine in a patient with thoracic as well as abdominal injuries.

A 63-year-old woman was admitted to Casualty after falling down the stairs at home. She had a ruptured stomach, and multiple fractured ribs on her left side, with a flail segment. There were no other associated injuries, and she was not severely shocked. Following initial resuscitation in Casualty, and surgical repair of her ruptured stomach in theatre, the trachea was extubated and the patient was transferred to the intensive care unit with a urinary catheter, an arterial cannula, a central venous catheter, and peripheral venous cannula in position. On arrival in the intensive care unit she was haemodynamically stable. Fluid restriction was used, humidified oxygen was administered by a face mask, and arrangements were made with the physiotherapy department for intensive chest physiotherapy. It was decided to use intrathecal morphine as the method of pain relief instead of intercostal nerve block, extradural morphine, or extradural bupivacaine.

Lumbar puncture was performed under strict aseptic conditions, with the patient in the lateral position. L3–4 and L4–5 spaces were chosen on alternate days. Following identification of the subarachnoid space with a 25-gauge spinal needle, 1 mg (1 ml) of preservative-free morphine was injected with physiological saline 4 ml through a bacterial filter. Following injection, the patient was kept supine for at least 1 h, and her respiratory and cardiovascular systems were monitored.

The patient experienced excellent pain relief throughout the 7-day period. Onset of analgesia usually took 15–20 min, and was complete in 45–60 min. The quality of the pain relief was such that the ends of the fractured ribs could be moved against each other without any discomfort whatsoever. The patient was able to cough, take deep breaths, and tolerate frequent vigorous chest physiotherapy. She was able to sit out of bed quite soon after her operation, and was ambulant at a very early stage.

Her cardiovascular and respiratory systems remained relatively stable (table I), her respiratory rate varying between

TABLE I. *Daily high and low values for Pa_{O_2}, Pa_{CO_2}, and respiratory rate*

Day	Pa_{O_2} (kPa)		Pa_{CO_2} (kPa)		Respiratory rate (b.p.m.)	
	(High)	(Low)	(High)	(Low)	(High)	(Low)
1	10.97	10.31	6.21	4.93	19	17
2	11.07	10.76	5.72	4.86	20	18
3	11.71	10.82	5.67	4.81	20	19
4	11.92	10.91	5.46	4.74	21	19
5	11.54	10.79	5.48	4.79	20	17
6	12.36	10.95	5.23	4.76	26	19
7	11.96	11.02	5.13	4.77	22	18

17 and 26 b.p.m., her Pa_{O_2} between 10.31 and 12.36 kPa, her Pa_{CO_2} between 4.14 and 6.21 kPa, and her arterial pressure between 110/60 and 140/90 mm Hg. Her colour remained good throughout, and she showed no signs of respiratory distress.

There are many arguments for and against tracheal intubation and mechanical ventilation in the treatment of thoracic injuries. However, in this case, it was decided not to ventilate the lungs, and the trachea was extubated following the surgical procedure in keeping with the criteria of Richardson, Adams and Flint (1982). Instead, our efforts were directed towards fluid restriction, humidification, pain relief, chest physiotherapy, and having the patient mobile as soon as possible after surgery.

Many techniques have been described for the management of fractured ribs, including intercostal nerve blockade, extradural bupivacaine and extradural morphine. Each technique has its own disadvantages. The disadvantage of intercostal nerve blockade is its relatively short duration of action, and the potential complication, albeit rare in experienced hands, of pneumothorax. Extradural morphine and extradural bupivacaine both carry the risk of damage to the thoracic segment of the spinal cord. Extradural bupivacaine also carries the risk of hypotension. On the other hand, systemic analgesic drugs may depress respiration as well as the cough reflex.

The potential complications of intrathecal morphine are well known. Its main risk is the development of delayed profound respiratory depression, which in unselected patients outside an intensive care unit tends to militate against its use. However, in selected cases, in an intensive care unit, provided that adequate care is given to patient selection, dosage and the avoidance of systemic opiates, this potential complication can be guarded against by careful monitoring of the respiratory system by vigilant medical and nursing staff. Other potential complications include urinary retention (10%), pruritus (2–5%), nausea, vomiting, anxiety or hallucinations, and meningitis, especially in cases of repeated administration. Even though all these potential complications have to be weighed up in each individual patient before a final decision is reached, I still feel that intrathecal morphine may have a place in the treatment of selected patients with multiple fractured ribs.

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ELECTRICAL ACTIVITY DURING INDUCED HYPOTENSION

Sir,—It seems odd to me that a conclusion of the paper entitled, "Electrical Activity of the Cerebral Cortex During Induced Hypotension in Man" (Thomas et al., 1985) is that a simple measure of total EEG power or filtered EEG voltage envelope (CFM) was shown to be a more *useful* monitor of cerebral electrical activity during controlled hypotension than measurements of power distribution in different frequency bands. I wondered if the authors could provide any evidence that, during anaesthesia where temporary hypotension is induced, any measure of EEG power correlates with patient outcome after anaesthesia. Not seeing such in their article, and not knowing of such myself, I believe that their conclusions are not merited by their data. Is there any correlation at any time—not only asleep, but also awake—between CFM changes and patient tolerance of hypotension from a standpoint of neurological function outcome? Furthermore, their statement that "this implies that direct cerebral monitoring is mandatory, should it become necessary to decrease arterial pressure below this value (60 mm Hg)" is not based on fact, but on an assumption, which has never, to my knowledge, been proven true. Could they share their data showing that this is true with us?

Further, how can editors allow such intermediate variables to be extrapolated to outcome variables? Don't you worry that allowing *speculation* the respectability of appearing as *fact* in such a respected journal as yours may mislead the naive reader?

M. F. ROIZEN
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REFERENCE

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Sir,—Thank you for allowing us to reply to the letter from Dr Michael Roizen.

Dr Roizen's views on the importance of relating clinical variables studied to outcome, on the avoidance of assumptions from intermediate variables and of the responsibilities of editors are well known (Litt and Roizen, 1984; Roizen, 1984).

Our study had two specific objectives: primarily to investigate whether the electroencephalographic differences between hypotension produced by sodium nitroprusside and by trimetaphan, demonstrated in the cat by Ishikawa and McDowall (1981), could be confirmed in man. Our secondary objective was to quantify the relationship between EEG and MAP and to define which features of the EEG were most highly correlated with decreases in arterial pressure in the majority of patients. It was *not* our aim to set up a study in man to demonstrate the predictive value of the EEG during controlled hypotension in terms of outcome.

There is adequate evidence that low brain perfusion produces measurable changes in cerebral electrical activity which can be correlated with clinical and neurological evidence of brain damage both in animals and man (Brierley et al., 1969; Malone, Prior and Scholtz, 1981). However, there is not, in our opinion, any definitive way by which patient outcome after induced hypotension could be adequately assessed without eventual systematic evaluation of brain histology by an experienced neuropathologist (Adams et al., 1966). Any "historical outcome" study would have to be substantial in terms of numbers and sophisticated neuropsychiatric tests before and after operation. Given the low morbidity and non-existent mortality of controlled hypotension in our hospital, there would be little chance of gaining adequate evidence.

Finally, we suspect that our concept of the word "useful" in this specific context is different to that of Dr Roizen on the other side of the Atlantic. The word was applied in our summary to contrast the effectiveness of two different ways of monitoring the EEG. It was not used as a measure of prediction of eventual neurological outcome.

P. V. Cole
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PRE-OXYGENATION

Sir—Drummond and Park (1984) looked at pre-oxygenation in normal patients. We have compared four deep breaths of oxygen with 5 min pre-oxygenation in 10 patients with lung disease (FEV_1 50% and below predicted for age, height, weight and sex). Ethics committee approval was obtained and patients

TABLE I. *Results, beginning with lowest* FEV_1. *Number in parentheses is percentage of normal predicted value.* * *Patients who achieved better* Pa_{O_2} *after 5 min quiet breathing of oxygen*

Patient No.	Age (yr)/Sex	FEV_1	VC	kPa			kPa			kPa			kPa		
				Pa_{O_2} air		4dbO$_2$	Pa_{O_2} air		4dbO$_2$	Pa_{CO_2} air		5minO$_2$	Pa_{CO_2} air		5minO$_2$
1	77F	0.7 (43)	0.95 (39)	5.9	→	20.5	6.8	→	25	4.4	→	4.9	4.5	→	4.9
2	64M	0.75 (24)	1.65 (41)	6.3	→	10.1	6.5	→	33*	8.9	→	8.7	8.9	→	10.1
3	71M	0.9 (34)	2.3 (67)	8.8	→	40.0	11.7	→	51	4.8	→	4.8	4.8	→	5.3
4	38M	0.96 (27)	1.1 (25)	6.3	→	8.8	6.3	→	10.7*	5.7	→	4.9	6.0	→	6.3
5	68M	1.1 (35)	3.8 (95)	11.3	→	28.8	11.7	→	53	4.8	→	4.5	4.8	→	4.8
6	79M	1.2 (36)	2.3 (52)	9.9	→	42.0	10.5	→	37	5.5	→	5.3	5.3	→	5.7
7	58M	1.25 (40)	1.8 (45)	7.9	→	12.5	7.7	→	37*	5.2	→	5.2	4.9	→	5.3
8	60M	1.3 (44)	1.8 (48)	10.0	→	39.0	11.1	→	31	5.2	→	4.5	4.8	→	5.6
9	63M	1.3 (40)	2.15 (53)	10.8	→	37.5	9.7	→	48	5.1	→	4.4	5.5	→	5.7
10	64M	1.45 (50)	2.2 (59)	9.6	→	36.0	—	→	38.7	5.9	→	4.4	—	→	5.9

had respiratory function tests before thoracotomy for carcinoma or pneumothorax. Patients were premedicated with temazepam by mouth and a cannula was inserted to the radial artery. Patients lay supine and had blood withdrawn for blood-gas analysis before taking four deep breaths of oxygen from a circle absorber receiving oxygen at 8 litre min^{-1}. Patients were exhorted to take as deep a breath as possible, and blood was sampled at the end of the fourth expiration. After a rest period blood-gas tensions were measured before and after 5 min quiet breathing with oxygen, after which patients were anaesthetized. As the efficacy of four deep breaths was unknown, the oxygenation methods were not randomized. Results are shown in table I. Patients 2, 4 and 7 were better off breathing oxygen for 5 min. All others achieved adequate arterial oxygen tensions for clinical purposes following four deep breaths of oxygen.

Arterial carbon dioxide tensions increased after 5 min quiet oxygen breathing ($P < 0.005$) and decreased after four deep breaths ($P < 0.05$) (paired t test).

Patients had not practised deep breathing before the study; some coughed during deep breathing. Deep inspiration is known to induce cough in patients with irritable airways (Gayrard et al., 1975). Patients with a hiatus hernia open the hiatus during a deep breath as observed on awake endoscopy (Skinner et al., 1972) and we wonder whether four-deep-breath oxygenation in pregnant patients, who have a high incidence of hiatus hernia, would predispose to reflux.

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Anika Rhodin
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OPIOID RECEPTOR BINDING AND ITS SIGNIFICANCE

Sir,—In your February 1985 issue there is a most interesting Editorial by Dr C. J. Hull concerning the opioid "receptor binding and its significance".

Speaking about "anaesthésie analgésique séquentielle" the author mentions deCastro as initiator of this technique (1968) and Rifat (1972) as the introducer of a "more conservative technique using smaller doses.." (of fentanyl and pentazocine).

I want to correct this last statement in supplying some information about our work with this method. Our first study on 165 patients using fentanyl 10–15 μg kg^{-1} and pentazocine 0.5 mg kg^{-1} was undertaken in September, 1969 and published in *Der Anaesthesist* (1970: **19**, 245). Rifat reported initially in October 1969 on the use, in 20 patients, of sequential anaesthesia with fentanyl 2–3 mg (with supplements of 0.25–0.50 mg) followed by pentazocine 60 mg at the end of anaesthesia, and then continued with an infusion containing an additional pentazocine 60 mg. This report was published in *Pain* by J. P. Paine and R. A. P. Burt in 1972. As can be seen, our paper reported on moderate doses of fentanyl and pentazocine while the dosage used by Rifat was far from conservative—approaching the figures proposed by deCastro. At the European Congress in Prague 1970 we, as well as Rifat, reported on our additional experiences with our respective methods. In 1982 at the European Congress in London, we reported on 2417 patients in whom we had used pentazocine 0.5–1 mg to counteract fentanyl in lower (2–8 μg kg^{-1}) and higher dosage (15–20 μg kg^{-1}) for inhalation and i.v. anaesthetics, respectively. From 1969 to 1985 a large number of anaesthetics were performed using pentazocine as a fentanyl antagonist. The results obtained were fairly constant so that, for 15 years, "sequentialization" has been in use in our country. This seems to be an interesting aspect supporting the more recent views concerning morphine receptors and ligands.

G. Litarczek
Bucharest

Sir,—I am most grateful to Dr Litarczek for drawing my attention to his early involvement in "anesthésie analgésique séquentielle". It is of particular interest that his initial studies involved the use of smaller doses than those reported by Rifat. I confess that I have regarded the technique to be largely of historical interest, and am fascinated to learn that it remains alive and well in Romania.

C. J. Hull
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CUTANEOUS REACTION TO PANCURONIUM

Sir,—Many anaesthetists have commented on the incidence of cutaneous reactions following i.v. administration of suxamethonium, tubocurarine (Stoelting, 1983) and atracurium (Rowlands, 1983). Not so many have reported cutaneous reactions following the administration of pancuronium.

A 19-year-old man was admitted for an arthroscopy of his left knee. He received pethidine 75 mg i.m. as a preanaesthetic medication 1 h before arrival at the operating room. He received pancuronium 0.75 mg i.v. before tracheal intubation facilitated by suxamethonium. Immediately after the injection of pancuronium, a localized erythematous reaction was noticed at the dorsum of the hand in which the i.v. cannula was placed. He also complained of itching. Haemodynamic values were normal. The reaction lasted for 15 min, and the patient was thereafter given halothane without complication.

Pancuronium causes very little histamine release, although allergic responses have been described (Heath, 1973).

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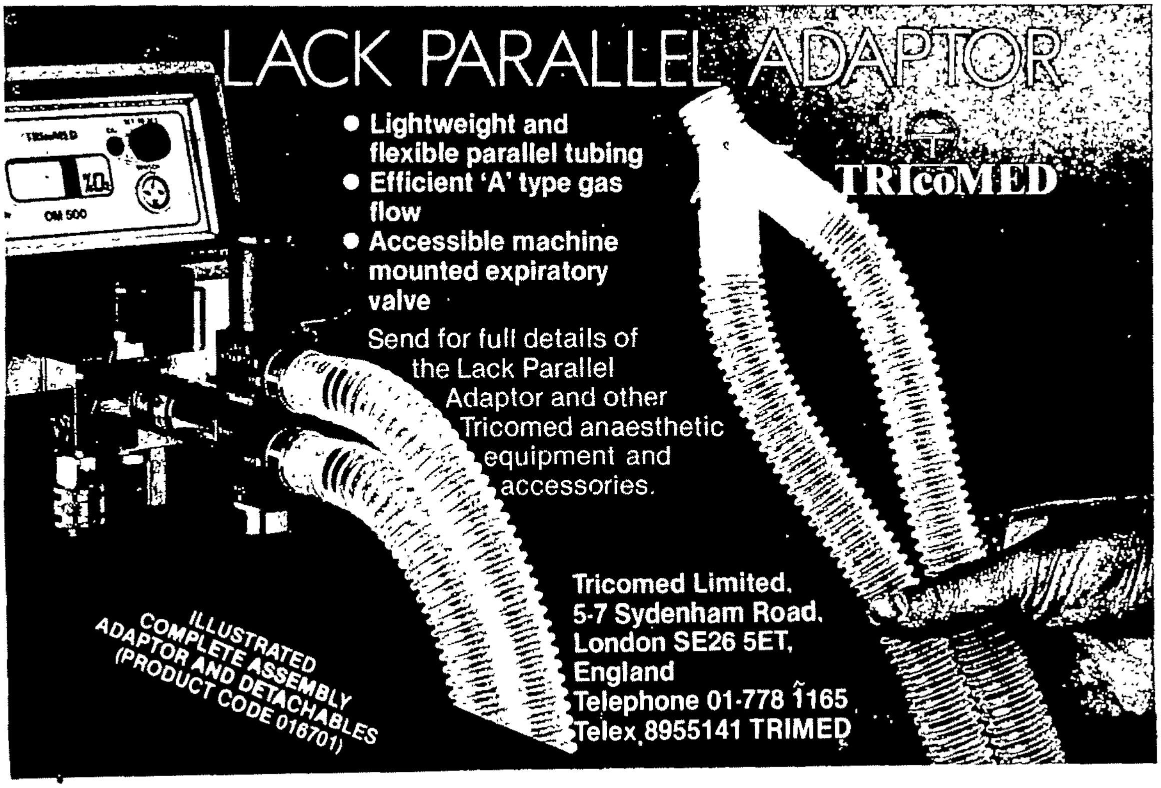

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